British Journal of Diseases of the Chest

EDITOR
† PHILIP ELLMAN
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Incorporating the British Journal of Tuberculosis and Diseases of the Chest

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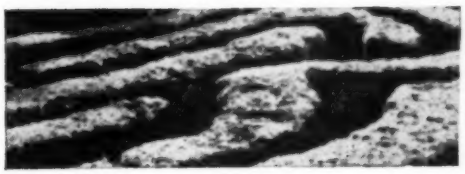

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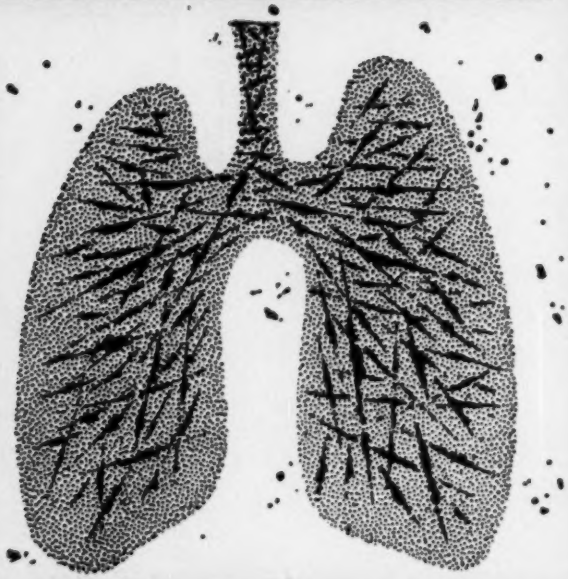

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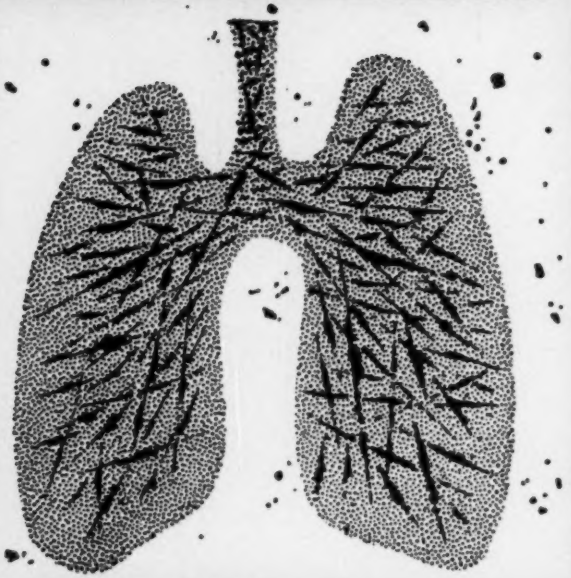

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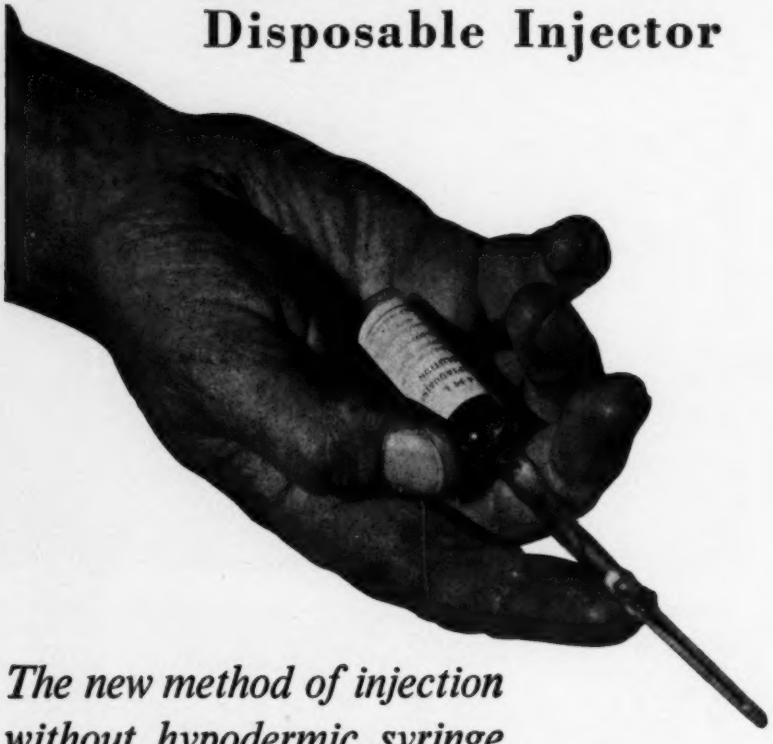

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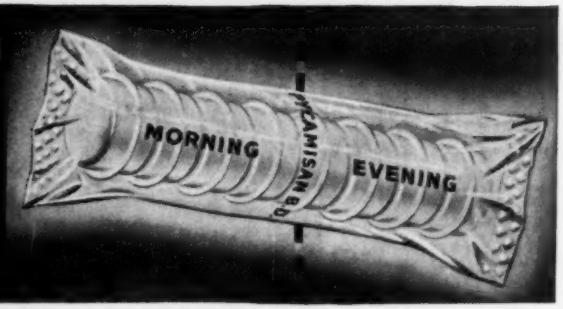

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To face first page of text

The publishers greatly regret to have to announce the death of Dr. Philip Ellman which occurred on May 10th. Dr. Ellman had been Editor of this Journal since October 1950, when he succeeded Dr. Clifford Hoyle. An obituary notice of Dr. Ellman appears on pages 290-291.

Brit. J. Dis. Chest (1960) **54**, 202.

HIPPOCRATIC FINGERS AND HYPERTROPHIC OSTEOARTHROPATHY

A STUDY OF 350 CASES

By Charles Coury

From the Department of Medicine, Hôtel Dieu, Paris

Clubbing of the digits is a feature common to simple " Hippocratic Fingers " and to " Hypertrophic Osteoarthropathy." Though closely connected, these two conditions must be considered separately from several aspects.

The former (H.F.) is a fairly frequent symptom, first mentioned by Hippocrates (fifth century B.C.), then by Aretius (second century A.D.), and much later by Pigeaux (1832). Except for some idiopathic or familial cases, H.F. are usually symptomatic of various chronic respiratory diseases, congenital heart defects with cyanosis, bacterial endocarditis, primary or secondary polycythemia; they may also develop occasionally with cirrhosis of the liver in children, chronic intestinal disease and diarrhœa, gastric stenosis, etc.

The latter (H.O.A.), first described in France by Pierre Marie (1890) and in Germany by Bamberger (1889), is much less frequent. It includes other symptoms besides clubbing: enlargement of the extremities, articular pain and swelling, and, above all, extensive periosteal thickening of the diaphysis of the bones, which can only be recognised on X-ray examination. Though H.O.A. may be associated with any of the same thoracic and extra-thoracic diseases as simple H.F. (including primary cases), malignant chest tumours—especially lung cancers and fibrous mesothelioma of the pleura—account for more than 90 per cent. of all typical cases.

As already mentioned, in spite of these and a few other discrepancies, H.F. and H.O.A. belong to a common group of peripheral disorders. These may be idiopathic, but are much more frequently closely connected with and highly significant of visceral diseases, particularly thoracic. Progressive conversion from simple H.F. to complete H.O.A. is sometimes noted. Moreover, intermediate conditions may be found, such as clubbing associated with moderate periostitis, simple clubbing combined with subacute rheumatic manifestations (*i.e.* " arthro-hippocratic syndrome ") (Bariéty and Coury, 1950), hypertrophic osteoarthropathy without joint manifestations, subacute rheumatism of thoracic origin, silent periostitis, etc.

In addition to H.F. and H.O.A., a third major condition has been described by Touraine, Solente and Golé (1935) under the name of " *Pachydermoperiostitis.*" It resembles H.O.A., but rheumatic pains are absent, while dermic thickening and seborrhœa of the forehead, nose and scalp are usually present (Fig. 7). No more than 60 cases have been published to date in the world literature, of which nine out of ten were idiopathic and appeared during childhood; yet in certain instances this condition was definitely recognised as secondary to a chest disease.

(*Received for publication January* 15, 1960.)

There is some confusion in relation to classification and nosology of H.F., H.O.A., pachydermoperiostitis and other related syndromes. Each should be precisely defined and labelled, since each is of great clinical significance as far as ætiology and prognosis are concerned. In 1946 and again in 1950 we suggested that the whole group should be known under the general term "dysacromelias," thus stressing an undoubted unity which is, nevertheless, consistent with particular and distinctive features. We have summarised this concept in a diagram (Fig. 1) which is now generally accepted by French writers. Presumably such particular conditions as silicotic arthritis (Caplan's syndrome), the so-called "shoulder-hand syndrome" and a few others might be placed within this comprehensive frame.

Our original material consists of 350 cases seen in a General Hospital and in a Chest Clinic over the past ten years or so. Two hundred and fifty of them are unselected and provide fairly accurate statistical data. This series includes

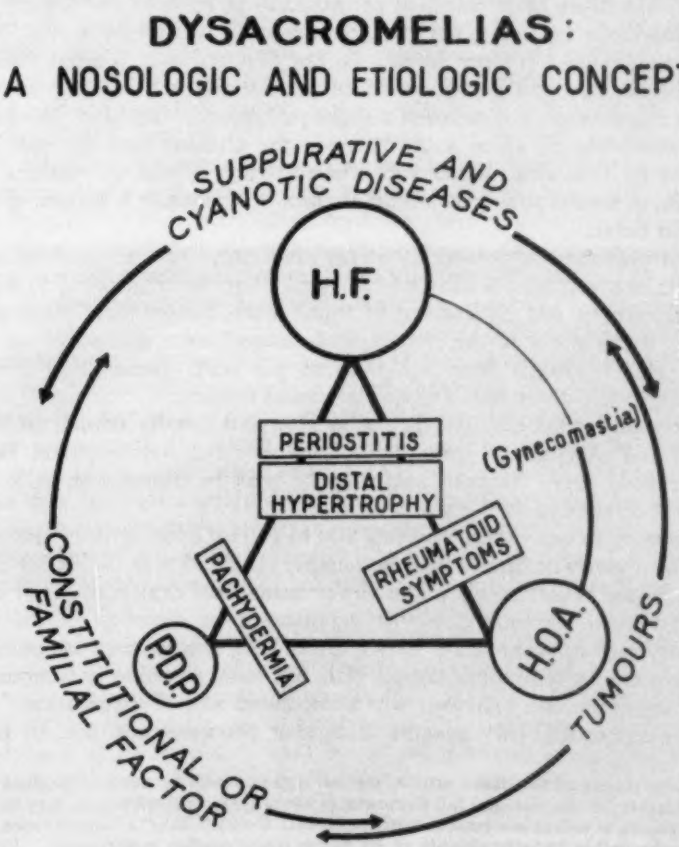

FIG. 1.

simple hippocratic fingers (76 per cent.), typical and complete hypertrophic osteoarthropathy (10·5 per cent.), arthro-hippocratic syndrome (7·5 per cent.), solitary periostitis (3 per cent.), solitary rheumatic syndrome of thoracic origin (1·5 per cent.), pachydermoperiostitis, primary and secondary (1 per cent.), simple clubbing with marked and extensive periostitis (0·5 per cent.).

Over 80 per cent. of the cases occurred in males.

Hippocratic Fingers

This morphological condition combines (1) bilateral curvature of the nails, and (2) enlargement of the soft structures, strictly confined to the finger-tips.

It may take on two different aspects: the fusiform type, with olive-shaped, drumstick or spindle-like finger ends; the clubbed type, with onion-shaped or watch-glass-like distal phalanges (Fig. 2).

Our cases have been classified as: minimal or even doubtful (± : 20 per cent.); moderate (+ : 41·5 per cent.); marked (++ : 26·5 per cent.); highly prominent (+++ : 12 per cent.). In the first group it is often difficult to state whether the nail curve should be considered as practically normal or whether it is actually indicative of a slight pathological clubbing. We have not found measuring the open angle between the phalanx and the nail bed, as suggested by Lovibond, Bigler and others (1938), helpful or reliable. Fixing the limits of true clubbing in minimal cases is ultimately a matter of clinical sense and habit.

Local cyanosis was present in 60 per cent. only and increased sudation of the digits in about 20 per cent. of our cases. Toes were involved to a greater or less degree in one patient out of four. Very limited and minimal bone changes (particularly in the proximal phalanges) were discovered on careful radiographic investigation in less than 20 per cent. Generalised cyanosis is found only when there are very special causal factors.

Purely unilateral clubbing is exceptional and usually related to localised vascular lesions (such as aneurysm of the limbs). Asymmetrical H.F. are comparatively more frequent and may be seen in conjunction with certain unilateral diseases of the chest.

According to our experience and that of several other writers, the ætiology of simple hippocratic fingers may be roughly classified as in Table I.*

In chronic bronchial infections the presence and degree of finger changes are not necessarily related to the significance or duration of the disease. Clubbing often appears at an early stage of lung abscess, and sometimes even as a premonitory symptom. Simple H.F. are more common in tumours of the chest than previously believed: when associated with " rheumatism " and/or extensive periostitis, they suggest malignant processes and are, in fact, the

* In the course of this short article, special attention will be devoted to chest diseases. Details, further information and full discussion of the subject, with references, may be found in previous papers as well as in a book recently published: Coury (Ch.), " L'Hippocratisme digital, l'Ostéo-arthropathie hypertrophiante et les autres dysacromélies apparentées." Baillière et Fils, éditeur, Paris, 1960 (with 53 illustrations).

PLATE X.

FIG. 2.—Marked clubbing of the fingers (grade + + +). Idiopathic H.O.A. in a male aged 55.
For comparison, the lower illustration shows a normal finger in a man of the same age.

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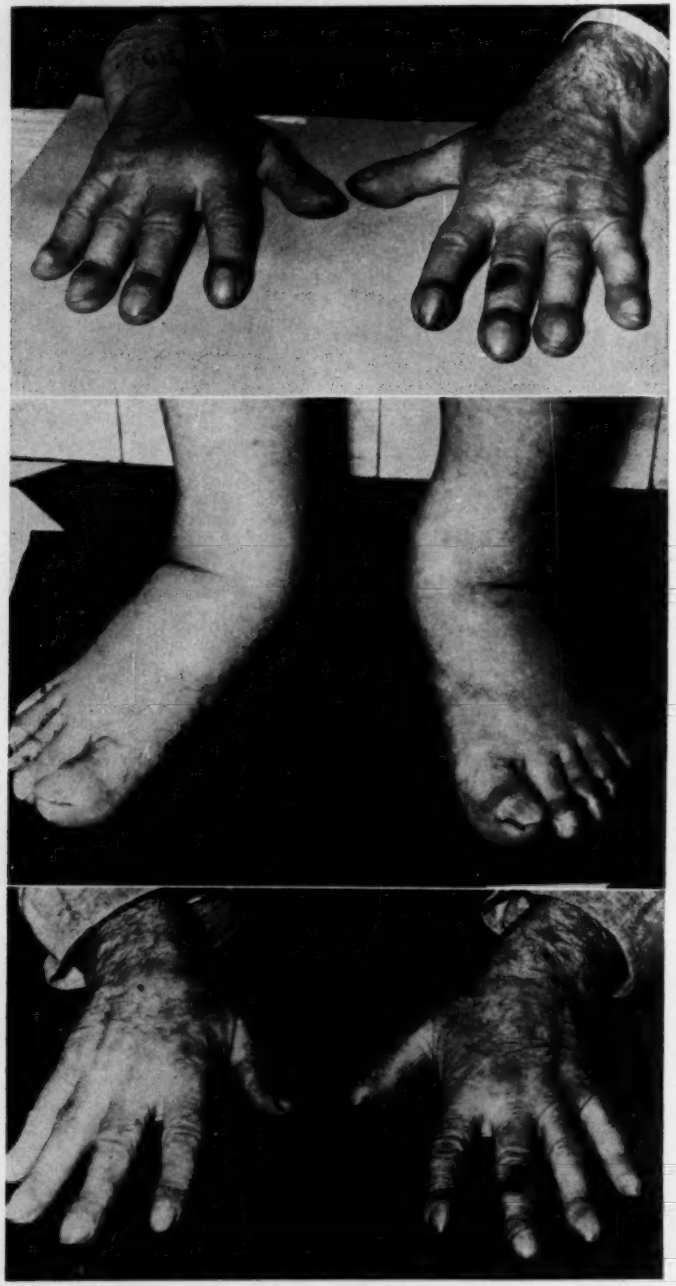

FIG. 3.—Enlargement of the extremities in secondary H.O.A. First clinical symptom in a case of squamous-cell bronchial carcinoma of the right lower lobe in a male aged 60.
(*Top*): Marked clubbing of the fingers (grade + + +) with thickening of the wrists.
(*Centre*): œdematous enlargement of the lower extremities, with clubbing of the toes.
(*Bottom*): Same patient, six weeks after surgical removal of the chest tumour. Marked regression of the finger clubbing. Articular pains stopped on the first day after operation.

TABLE I.—ÆTIOLOGY OF SIMPLE CLUBBING (HIPPOCRATIC FINGERS)

	Type of the disease	*No. of unselected cases of H.F. secondary to the disease (per cent.)*	*No. of cases of H.F. to be expected in the disease (per cent.)*
Respiratory: 80%	Bronchiectasis and Bronchorrhœa ..	25–30	20–30
	Cancer of the Lung (Primary or Secondary)	15–20	3–4 (as an early symptom) 15–25 (in the course of the disease)
	Tuberculosis	10–20	20
	Lung Abscess and other non-tuberculous Suppurations	10–15	20
	Pulmonary Fibrosis (Secondary or Primary). Lung Cysts. Miscellaneous ..	6–10	75: Arterio-venous fistulæ 70—75: Primary fibrosis 10: Lung cysts 5–6: Pneumoconiosis
	Mediastinal tumours	4–5	2–4
	Empyema	2–3	
Cardio-vascular and Extra-thoracic: 10–15%	Congenital Heart Defects (with Cyanosis)	5–10	80–95
	Cirrhosis of the Liver, Chronic Diarrhœa and other abdominal conditions ..	5–6	8–10
	Osler's Disease (Subacute Bacterial Endocarditis). Heart failure	4–5	25–50
Idiopathic: 5–10%	Primary or Familial cases	5–10	

precursors of complete and typical H.O.A. Clubbing in tuberculous patients, when present, is as a rule minimal and develops mostly in cases with old fibrosis and cavitation. Chronic empyema is to-day an unusual cause of H.F., while lung sclerosis of different types and shunts in the pulmonary circulation may play an important rôle.

HYPERTROPHIC OSTEOARTHROPATHY

Complete hypertrophic osteoarthropathy,* or Pierre Marie and Bamberger's disease, the second of the main types of dysacromelia, is a comparatively rare condition. The name should only be given to primary or secondary syndromes which combine the five following symptoms:

(1) *Hippocratic fingers*, usually marked, with involvement of the toes (Fig. 3).

(2) *Hypertrophy of the upper and lower extremities*, more or less similar to that of acromegaly, but predominating in the soft structures and confined to the

* Often called also "pulmonary" or "pneumonic," owing to its usual relation to respiratory disorders.

distal portions (fingers, hands and wrists; feet, ankles and lower third of the legs, where it may simulate localised chronic œdema or even elephantiasis) (Fig. 3). As a rule the head is wholly normal, although the facial features may sometimes be slightly prominent (30 per cent. of our cases).

(3) *Joint manifestations*, including dull or severe pain and local swelling, resistant to usual treatment; on the whole the picture is of a symmetrical subacute inflammatory rheumatic condition, involving ankles (88 per cent.), wrists (82·5 per cent.), knees (75 per cent.), and even elbows (17 per cent.), shoulders (9·5 per cent.) or fingers (7 per cent.). Articular signs are frequently an early or even premonitory symptom, so that any unusual rheumatoid syndrome necessarily implies a careful and thorough investigation of the chest cavity (Ellman, 1953).

(4) *Bone changes* consisting of bilateral proliferating periostitis, involving the diaphysis of the radius and ulna (80 per cent.), tibia and fibula (respectively 74 and 80 per cent.), upper phalanges (60 per cent.), femora (about 50 per cent.), metacarpus, metatarsus (about 40 per cent.), humerus, lower phalanges (about 25 per cent.), pelvis (6·5 per cent.) (Fig. 4). The skull and other bones are practically always normal. This special type of periostitis is a basic symptom of H.O.A. Radiologically it is seen either as a narrow, regular and finely laminated sheath of variable length along the shaft of the bone (Fig. 5), or as a compact layer, but irregularly ridged, like wax dripping along a candle. Both pictures are often combined in the same patient. The periosteal growth may also take on a different appearance (Fig. 6), such as a pincushion or a mushroom-like excrescence, seamed or like a paintbrush, etc. The epiphyseal structures and the joints are not affected. Moderate diffuse decalcification was present in about 55 per cent. of our cases.

(5) *Moderate peripheral neuro-vascular disorders* are very common, such as local cyanosis, limited areas of hypersudation, paræsthesia, chronic erythema, oscillometric changes, etc.

Several clinical pictures are discernible, according to the dominant symptom. Incomplete forms are not uncommon and different intermediary conditions establish the relationship between simple H.F., typical H.O.A. and secondary pachydermoperiostitis.

Complete H.O.A. is secondary to malignant tumours of the chest in more than 90 per cent. of the cases. Lung cancers account for about 80 per cent.; these may be metastatic or primary (especially the squamous-cell type of bronchial carcinoma). Mesothelioma as well as fibrosarcoma and fibroblastic tumours of the pleura or sub-pleural space account for about 10 per cent., while other chest tumours (various mediastinal tumours, Hodgkin's disease, benign growths) are found in less than 5 per cent. Another 5 per cent. may be attributed to chest diseases other than tumours, extra-thoracic causes and primary forms.

H.O.A. is to be expected in 3 or 4 per cent. at least of all lung cancers, and often as an early and highly significant symptom. According to Wiermann *et al.* (1954), H.O.A. would be present in 60 per cent. of fibrous tumours of the pleura.

Dysacromelias and Gynecomastia

As stated by Bariéty and Coury (1950) ten years ago and confirmed since by others, a little over 5 per cent. of all types of dysacromelias occurring in males are associated with moderate bilateral gynecomastia. This association is far more frequent with solitary periostitis and with H.O.A. (about 30 per cent.) than with simple H.F. (less than 1 per cent.). Hypertrophy of the mammary gland is rarely an early symptom. Gynecomastia combined with H.O.A. or with silent periostitis is highly suggestive of intrathoracic malignant disease.

Laboratory Investigations

To date no laboratory investigations have achieved positive results, either diagnostically or in elucidating the pathogenesis of the dysacromelias.

Contrary to what has sometimes been said, the increase in the number of red or white cells is not directly connected with the mechanism of clubbing and is merely a consequence of some causal disease. Though H.F. are very common in primary and secondary polycythemia with or without cyanosis, they may develop as well in patients with marked anæmia. It should also be noted that cases of severe polycythemia and cyanosis do not necessarily lead to dysacromelia. When present, an increased sedimentation rate, a slight fall of the blood proteins, a moderate rise of the $\alpha 2$ and γ globulins, should be considered as a common sign of an inflammatory process. In most cases the calcium phosphorus balance is normal, as also the alkaline phosphatase activity. Bariéty *et al.* have lately (1960) reported that acid phosphatase activity is moderately increased in more than 60 per cent. of all dysacromelias (ranging between 5 and 10 Plumel units), and especially in those cases related to bronchiectasis or cancer. Urinary steroid elimination is usually low, particularly in cases associated with gynecomastia.

The rate of O_2 blood-saturation in the peripheral arteries is within normal limits in rather more than 50 per cent. of all unselected cases; it is naturally low when H.F. are associated with congenital heart disease or with other severe anoxæmic processes, but this does not imply a cause-and-effect relationship and clubbing is by no means proportionate to arterial anoxæmia. In the same way, CO_2-tension in the arterial blood and O_2-tension in the venous blood vary according to causal factors. This applies also to respiratory function, acid-base determination, electrocardiography, intracardiac pressures and various other measurements.

General Remarks on the Clinical Significance, Course and Prognosis of Dysacromelias

The clinical importance of H.F., H.O.A. and related conditions, as well as their value in the diagnosis of chest diseases, are well known and need not be considered in this paper.

With regard to chest disease two practical rules should be emphasised once again: *the closer the condition is to simple clubbing of the terminal phalanx, the more likely is a chronic infectious or fibrotic disease to be the cause.* On the other hand, *the*

closer the syndrome is to complete H.O.A., with joint manifestations and typical periostitis, the more a malignant or fibrous tumour should be suspected; associated gynecomastia is still more indicative of malignant disease.

It is now well known that *the course of H.F. and H.O.A. is closely conditioned by whatever may be the causal disease.*

The clinical onset of the dysacromelia generally follows that of the thoracic disease, which may be concurrent. The peripheral syndrome may also appear long before the first chest manifestation, notably in malignant conditions: the dysacromelia should then be recognised without delay, to allow an early diagnosis of the chest condition.

Variation in the intensity of the distal symptoms only occurs where the causal factor itself is liable to fluctuations, whether spontaneously or owing to treatment. The dysacromelic syndromes only improve and disappear provided the primary disease does so. In H.O.A., the surgical removal of the tumour is followed by almost immediate relief of the joint pains and swelling; the œdematous enlargement of the extremities and the associated gynecomastia fade progressively after a few days or weeks, and the finger clubbing disappears after a few months (Fig. 3); the regression of bone changes is always very slow and incomplete. Extrathoracic metastases do not cause dysacromelias, so that a relapse of the peripheral troubles means a local relapse of the chest tumour.

The only effective treatment is that of the causal disease. Usual antirheumatic drugs are generally useless. Hormonotherapy secures a temporary and incomplete relief of the arthralgias. Unilateral vagotomy, as suggested by Brea (1947), Hansen (1952), Flavell (1956), and Huckstep and Bodkin (1958), appears to be a useful procedure, but the results claimed have not yet been confirmed: our single attempt on these lines has been a failure.

Pathological Physiology

The pathogenesis of H.F. and H.O.A. remains tiresomely uncertain, as no satisfactory answer has yet been given to this puzzling problem as a whole, nor is any one explanation applicable to all cases. An extensive review of old and modern theories pertaining to the mechanism of dysacromelias has been attempted in some of our previous papers.

It is now generally admitted that the *local process* is connected with functional changes affecting the precapillary circulation in the extremities: this is unquestionable in relation to the soft structures of the finger ends in simple clubbing; it seems also most likely in the vicinity of the periosteal layer in H.O.A., as demonstrated in two of our cases (Fig. 8).

Most writers also believe that the common *visceral alteration* in almost all the causal diseases lies in vascular shunts in the pulmonary circulation (of the arterio-venous or arterio-arterial type), or in some physiological equivalent.

The pathogenesis between the thoracic starting-point and the distal receiving-point is a matter for conjecture. Whether it should be attributed to blood changes or to some nervous effect (*i.e.* vagal or sympathetic) is uncertain, or to the possible participation of an endocrine imbalance, such as moderate hyperpituitarism. Anoxæmia and polycythemia are not constant factors. Hall

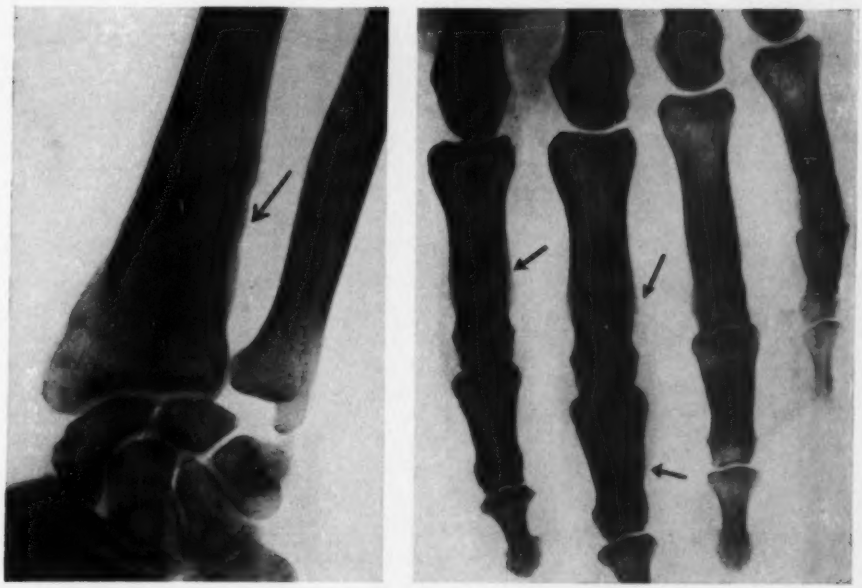

FIG. 4.—Moderate periostitis of the radius and ulna (*left*) and of the finger phalanges (*right*) in a case of secondary H.O.A. symptomatic of a chronic lung abscess; male, aged 53.

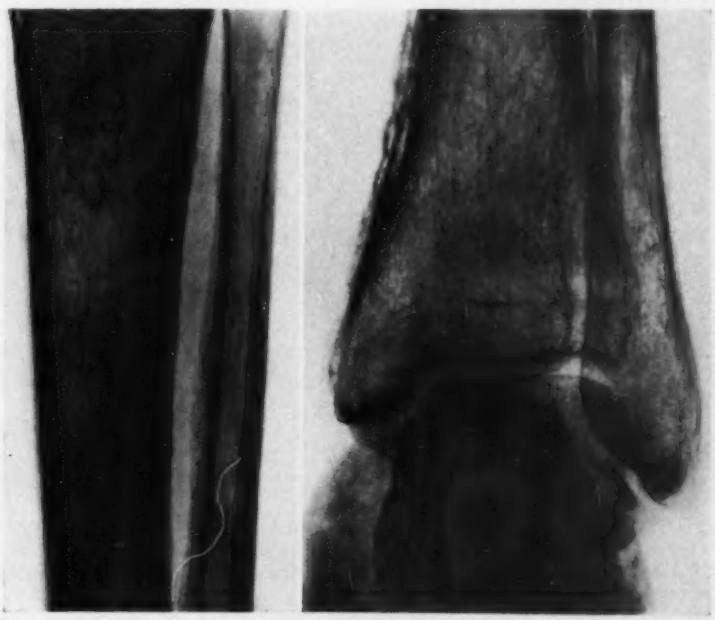

FIG. 5.—Marked periosteal reaction of the tibia and fibula in two cases of secondary H.O.A.

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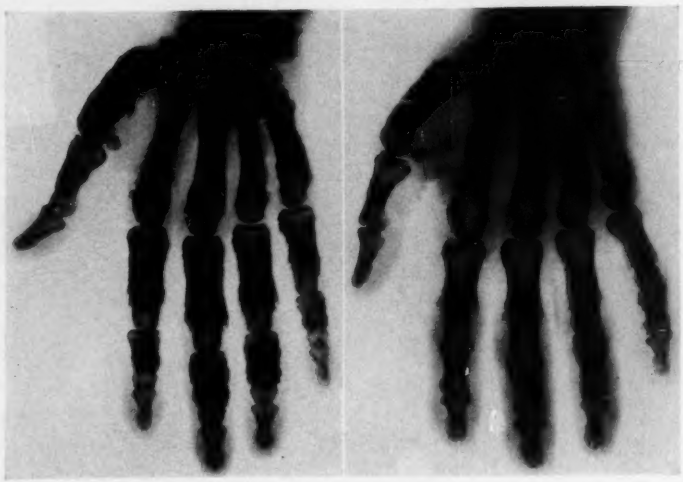

FIG. 6.—Marked periosteal reaction of the metacarpus and phalanges in two severe cases of secondary H.O.A.

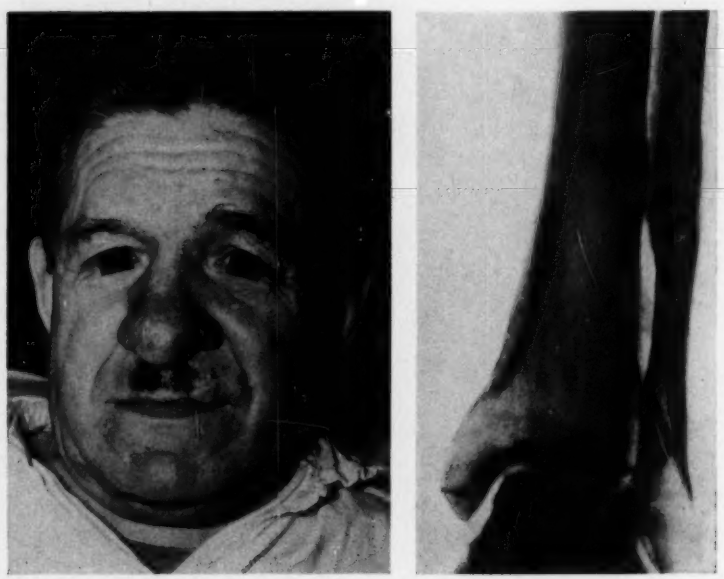

FIG. 7.—Primary pachydermoperiostitis in a male aged 61.
Onset at the age of 18.
(*Left*): Thickening of the skin of the forehead and nasal seborrhœa (with rhinophyma).
(*Right*): Compact layer of periostitis along the shaft of the tibia and fibula.

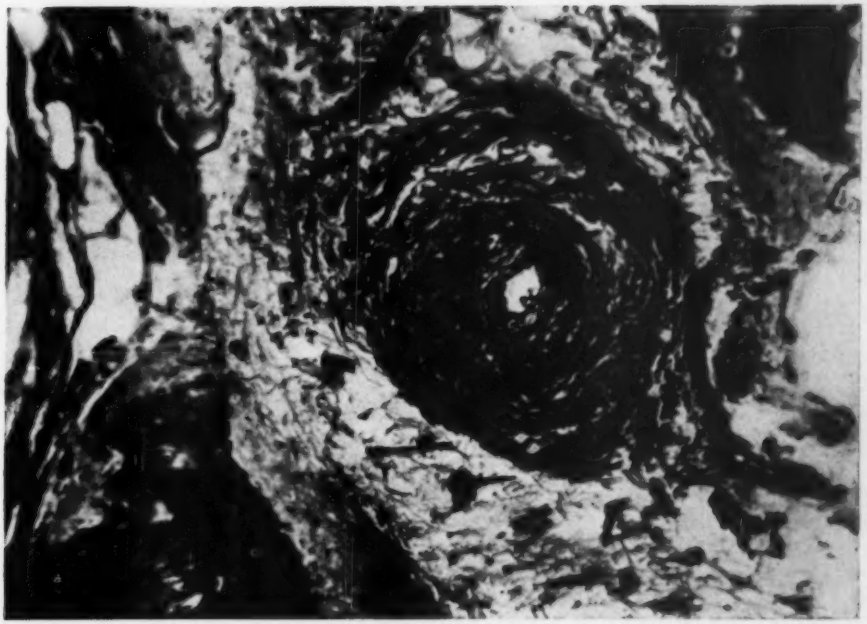

FIG. 8.—Arterio-venous precapillary anastomosis close to the periosteal proliferation. Muscular hypertrophy of the arteriolar wall (glomus-type) acting as a sphincter. Surgical biopsy of the tibia in a case of secondary H.O.A. symptomatic of a primary cancer of the lung.

(1959) has recently suggested that a high rate of reduced ferritin, following incomplete oxydation because of the pulmonary shunts, might lead to an opening of the digital anastomoses: this original and interesting theory still needs to be confirmed. A major fact to be considered is that dysacromelias do not develop regularly in all patients suffering from the usual causal diseases, but mostly in those who show a definite *predisposition* (such as a slight constitutional curving of the nails in simple clubbing, or a moderate enlargement of the extremities in H.O.A.): this natural tendency might well be connected with some genetic factor, implying a potential activity of the anterior lobe of the pituitary gland, but so far no convincing proof of this has been obtained.

The practical significance of dysacromelias as well as the uncertainty of their mechanism should encourage further research on the part of clinicians and physiologists.

Summary

Hippocratic fingers and hypertrophic osteoarthropathy belong to a common group of peripheral disorders. Together with pachydermoperiostitis they may be idiopathic but are all highly significant of visceral, particularly intrathoracic, disease.

Three hundred and fifty cases of these so-called dysacromelias are reviewed. The thoracic disease usually precedes the dysacromelia and the progress of the two conditions is closely associated.

The pathogenesis of dysacromelias and their mechanism are not yet established.

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TIMED VITAL CAPACITY

A CORRELATION WITH MAXIMAL BREATHING CAPACITY AND USE AS A CLINICAL TEST OF VENTILATORY FUNCTION

By George C. Leiner, Maurice J. Small, and Sol Abramowitz

From the Cardio-Pulmonary Laboratory, Veterans Administration Hospital, East Orange, New Jersey

Introduction

Ventilatory function is usually estimated by measuring vital capacity and maximal breathing capacity (M.B.C.). The disadvantages of determining M.B.C. have been discussed repeatedly. They are: a special machine and a trained physician or technician must be available; the test requires much co-operation from the patient and cannot be performed by very sick patients; in a patient suffering from bronchial asthma it may provoke an asthmatic attack. Attempts were therefore made to find another test which would give the same information as obtained from the M.B.C. Tiffeneau and Pinelli (1947, 1948) described a method which does not have the disadvantages of the maximal breathing capacity test. With the aid of a recording spirometer they measured the " capacité pulmonaire utilisable à l'effort " (C.P.U.E.), that is the volume of air exhaled in the first second of a forced vital capacity determination. They found this volume to remain remarkably constant in the same subject. This test became known as the " Tiffeneau test." Tiffeneau, Bousser and Drutel (1949) found the C.P.U.E. to be between 30 and 95 per cent. of the vital capacity for the whole group, and in normals above 80 per cent. They thought that the determination of the C.P.U.E. could replace the measurement of the M.B.C., since calculation of the M.B.C. seemed to be possible from the C.P.U.E. They stated that the M.B.C. can be obtained approximately by multiplying C.P.U.E. by 30. Cara (1953) called this the indirect M.B.C.

Gaensler (1951) devised a modified vital capacity spirometer which makes measurement of a timed expiratory volume and of the total vital capacity easy. Timed vital capacity studies with the use of the " vitalometer " have become routine procedures in many pulmonary function laboratories. Usually the volumes exhaled in the first one, two and three seconds of a vital capacity determination are measured and then reported as a percentage of the total vital capacity. According to Gaensler the normal mean values are: for the first second 83 per cent., for the first two seconds 94 per cent., for the first three seconds 97 per cent. The normal values for the one second are between 72 and 92 per cent. Gaensler also stated that in restrictive ventilatory insufficiency the timed vital capacity is normal in the presence of a reduced total vital capacity; in obstructive ventilatory insufficiency the timed vital capacity is considerably diminished without marked reduction of the total

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vital capacity. He found a good correlation between the one second vital capacity and the M.B.C. expressed as a percentage of predicted, the coefficient, *r*, being 0·88±0·06. Simonon and co-workers (1954) observed a less satisfactory correlation. According to van Veen and Hirdes (1952) there is a good correlation between the one timed vital capacity and the residual volume in percentage of vital capacity.

Kennedy (1953) suggested that the 0·75 second vital capacity be measured because this permitted the most reliable calculation of the M.B.C. Needham and co-workers (1954, 1955) were of the opinion that the M.B.C. could be predicted most reliably from the two-second vital capacity. D'Silva and Kazantzis (1954) pointed out that the performance of the M.B.C. and the timed vital capacity are, to a certain degree, dependent on the observer; each laboratory should therefore determine its own normal values. Miller and co-workers (1956) recommended the 0·5 second vital capacity as the most sensitive index of ventilatory function. Bernstein and Kazantzis (1954) criticised the methods of predicting M.B.C. from the expiratory fast vital capacity curve and described a method of doing so from expiratory and inspiratory fast vital capacity curves. Bell and Howell (1955) came to the conclusion that the analysis of the timed and total vital capacity is useful as a screening test because of its simplicity, reliability and sensitivity. Pemberton and Flanagan (1956) found the one-second timed vital capacity to be independent of age, height and weight; according to their investigations, the mean one-second timed vital capacity is 79·1 per cent. of the total vital capacity, with a standard deviation of ±7·2. On the basis of these figures they stated that values below 65 per cent. have to be considered pathological. Attinger and co-workers (1958) believed that the M.B.C. is a better test than the timed vital capacity because it is affected by inspiration and expiration.

From this review of timed vital capacity studies it can be seen that such studies are of value in the pulmonary function laboratory, although there is some difference of opinion as to their significance. We therefore thought it of interest to present our own observations collected over a period of four years.

Methods

Maximal breathing capacity as well as vital capacity tests were made in most patients referred to our pulmonary function laboratory during the past four years. The M.B.C. was determined, using a 9 litre Collins respirometer, directional valves and soda lime container removed. Timed vital capacity studies were done with the Gaensler-Collins vitalometer (Gaensler, 1951).

The following report is based on observations made on a series of 400 consecutive tests on 400 subjects. They were patients with various chronic pulmonary diseases.

Results

We divided the total number of 400 patients into four groups on the basis of their one-second vital capacity as a percentage of total vital capacity on one

axis and on their percentage of predicted vital capacity on the other axis, following a similar scheme presented by Bell and Howell (1955) and the data given by Thomson and Hugh-Jones (1958). We assumed as normal a vital capacity of more than 90 per cent. of what was predicted for the respective individual; and we assumed as normal a one-second timed vital capacity of more than 70 per cent. of the total vital capacity. A restrictive ventilatory defect is present when the vital capacity is below 90 per cent. of the predicted value while the one-second timed vital capacity is normal. An obstructive ventilatory defect is characterised by a decreased one-second timed vital capacity in the presence of a normal total vital capacity. Combined obstructive and restrictive ventilatory defects are defined by the following: Total vital capacity and one-second timed vital capacity are diminished.

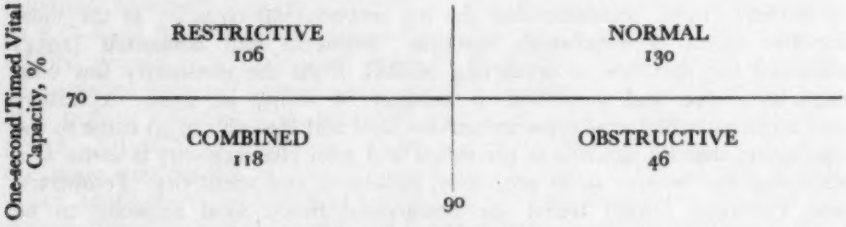

FIG. 1.—Classification of 400 cases on basis of their total vital capacity in percentage of predicted vital capacity and their one-second timed vital capacity in percentage of total vital capacity.

In Fig. 1 the groups are presented according to these criteria. One hundred and thirty individuals belong to the " normal " group; 106 to the " restrictive " group; 46 to the " obstructive " group and 118 to the " combined " group.

For each group we calculated the ratio: maximal breathing capacity, L. per minute/one-second timed vital capacity, L. The means and standard deviations of the means are given in Table 1.

TABLE 1.—MEANS AND STANDARD DEVIATIONS OF THE MEANS FOR THE RATIO: MAXIMAL BREATHING CAPACITY, L./MIN. / ONE-SECOND TIMED VITAL CAPACITY, L.

	Normal	*Restrictive*	*Obstructive*	*Combined*
M.B.C., L./min. / 1 second T.V.C., L.	36·3 ± 6·29	39·7 ± 6·63	33·8 ± 5·91	33·0 ± 8·36

Table 2 shows the significance of the differences of the means between the four groups for the ratio: maximal breathing capacity, L. per minute/one-second timed vital capacity, L. The differences are considered statistically significant when $P<0.05$.

The " restrictive," the " obstructive " and the " combined " groups differ

significantly from the " normal " group. The " restrictive " group differs significantly from the " obstructive " and the " combined " group. There is no significant difference between the " obstructive " and " combined " groups.

TABLE 2.—SIGNIFICANCE OF DIFFERENCES OF MEAN, P, OF THE RATIO: $\frac{\text{M.B.C., L./MIN}}{\text{ONE-SECOND TIMED VITAL CAPACITY, L.}}$ BETWEEN THE FOUR GROUPS

	Normal	*Restrictive*	*Obstructive*
Normal	—		
Restrictive	<0·001	—	
Obstructive	<0·02	<0·001	—
Combined	<0·001	<0·001	<0·05

Fig. 2 shows the ratio: maximal breathing capacity, L. per minute/one-second timed vital capacity, L., in relation to the percentage frequency, in each of the four groups.

It can be seen that in spite of the significant differences for the ratio between the groups there is a wide variation of the ratio in each group. On the basis

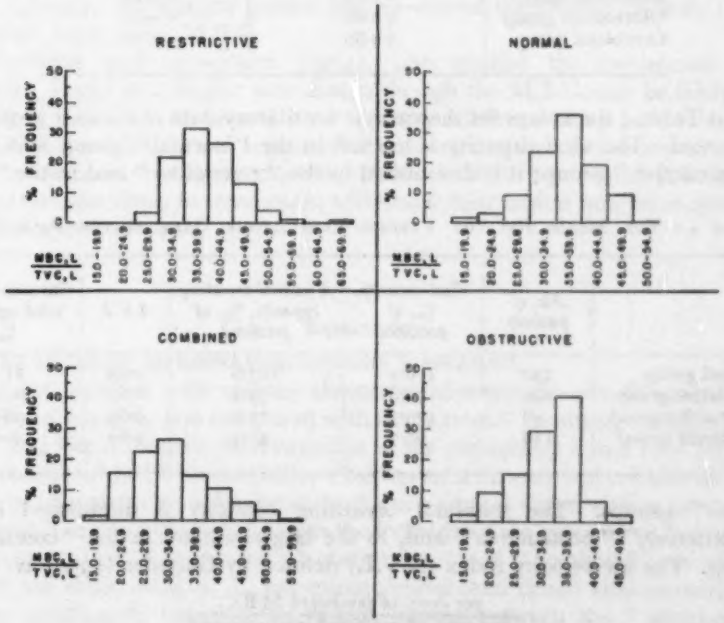

FIG. 2.—The ratio: $\frac{\text{maximal breathing capacity, L./minute}}{\text{one-second timed vital capacity, L.}}$ in relation to the percentage frequency, in each of the four groups.

of this observation it appears clearly that in a single case the M.B.C. cannot be calculated from the one-second timed vital capacity.

If the ratio: maximal breathing capacity, L. per minute/one-second timed vital capacity, L., is calculated for the 400 observations, a mean value of 35·9 is obtained. This comes close to the factor of 35, which is most generally used (Gandevia and Hugh-Jones, 1957), and is slightly lower than the factor of 37 suggested on theoretical grounds by Cara (1953).

In Table 3 the coefficients of correlation between the one-second vital capacity in percentage of total vital capacity and the M.B.C. expressed in percentage of predicted are presented. All coefficients of correlation are significant at the 5 per cent. level or below.

TABLE 3.—COEFFICIENTS OF CORRELATION, *r*, AND LEVEL OF SIGNIFICANCE, *P*, BETWEEN THE ONE-SECOND VITAL CAPACITY IN PERCENTAGE OF TOTAL VITAL CAPACITY AND THE M.B.C. EXPRESSED IN PERCENTAGE OF PREDICTED

	Coefficient of correlation, r	*Level of significance, P*
Complete group	±0·86	<0·01
Normal group	±0·40	<0·01
Restrictive group	±0·22	<0·05
Obstructive group	±0·66	<0·01
Combined group	±0·89	<0·01

In Table 4 the means for the various ventilatory data of the four groups are presented. The vital capacity is normal in the " normal " group and in the " obstructive " group; it is diminished in the " restrictive " and in the " combined " groups. The maximal breathing capacity is diminished in the " restrictive," " obstructive " and, to the largest extent, in the " combined " group. The air velocity index (A.V.I.) defined by Gaensler (1950) as

$$\frac{\text{per cent. of predicted M.B.C.}}{\text{per cent. of predicted vital capacity}}$$

is at the upper limit of normal in the " restrictive " group and considerably diminished in the " obstructive " and " combined " groups.

TABLE 4.—THE MEANS FOR THE VARIOUS VENTILATORY DATA OF THE FOUR GROUPS

	No. of patients	*Vital capacity, %, of predicted*	*Maximal breathing capacity, %, of predicted*	*A.V.I.*	*One-second timed vital capacity, %*
Normal group	130	106·2	107·6	1·02	81·1
Restrictive group	106	70·8	79·4	1·13	81·2
Obstructive group	46	105·3	72·9	0·69	58·0
Combined group	118	65·7	41·7	0·63	50·8

Discussion

The measurement of the one-second timed vital capacity with the Gaensler-Collins vitalometer is an easy and reliable procedure for obtaining information on ventilatory function. The routinely performed estimation of the maximal breathing capacity is more complicated than performance of the timed vital capacity. It would therefore be advantageous if determination of timed vital capacity could replace that of the maximal breathing capacity.

In order to evaluate the significance of timed vital capacity determinations a comparison of these with maximal breathing capacities was done in 400 individuals with various chronic pulmonary diseases.

The whole group was divided into " normals," and individuals with " restrictive," " obstructive " and " combined " ventilatory defect. The ratio: maximal breathing capacity, L. per minute/one-second timed vital capacity, L., was calculated for each individual. Although this figure differs significantly for the mean of each group, there was overlapping between the groups. The ratio for the whole group is in the same range as that found by others. From these studies it appears that in a single case the maximal breathing capacity cannot be calculated from the one-second vital capacity volume with exactitude. However, for practical purposes, the ratios are not too different and it may be permissible to calculate the M.B.C. from the volume of the one-second vital capacity. For clinical studies the one-second timed vital capacity could, therefore, replace the M.B.C.

Needham and co-workers (1954), who studied the two-second vital capacity, found in a similar way that, although the M.B.C. can be fairly well predicted from the two-second vital capacity volume, it may be unnecessary to predict the M.B.C. and suggested the use of the timed vital capacity as a valid measure of ventilatory capacity. If the facilities are available both tests should be done since, in some cases, additional information may be so obtained (Snider and co-workers, 1955).

Summary

The literature on timed vital capacity is reviewed.

In 400 patients with various chronic pulmonary diseases the one-second timed vital capacity was compared with the maximal breathing capacity.

It was found that the determination of the one-second timed vital capacity with the aid of the Gaensler-Collins vitalometer is an easy and reliable method.

A good correlation exists between the one-second timed vital capacity and maximal breathing capacity. When the individuals are grouped as " normal " and patients with " restrictive," " obstructive " and " combined " ventilatory defect, the ratio: M.B.C., L. per minute/one-second timed vital capacity, L., differs significantly between the groups, except between the " obstructive " and " combined " groups. For clinical evaluation of ventilatory function the determination of the one-second timed vital capacity appears to be satisfactory.

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THE SOLID SARCOMATOUS PULMONARY ARTERY

JOHN E. JACQUES AND ROBERT BARCLAY

From the London Chest Hospital and the City Hospital, Nottingham

WE have recently encountered in two patients the finding at thoracotomy of a solid pulmonary artery. In both the pre-operative diagnosis was of primary pulmonary neoplasm, and the ultimate histological diagnosis was of sarcoma occupying the whole lumen of the main pulmonary artery with extension along its branches. In retrospect, we believe it may be possible to make a correct pre-operative diagnosis in this uncommon condition.

At least eight such cases have already been reported. Durgin and Ingleby (1946) collected six and considered the primary sarcoma had arisen in the pulmonary artery in each. A further case of chondrosarcoma, which eventually filled both main pulmonary arteries, was reported by Lowell and Tuky (1949). In a comprehensive review of cardiac tumours, Pritchard (1951) describes a case of intra-luminal myxosarcoma of the pulmonary artery in a man of 32. At autopsy a further finding was a myxosarcoma of the right ventricle, arising from the septal wall. This case bears considerable resemblance to Case 2 (below).

Case Reports

CASE 1. A woman aged 54 was admitted to the City Hospital, Nottingham, in May 1958 with a history of increasing dyspnœa on effort and a productive cough persisting after a pyrexial illness some eighteen months previously. In July 1957 her sputum had been positive for Acid Alcohol Fast Bacilli, since when she had received continuous antituberculous chemotherapy. At that time (1957) her X-ray had shown a cavity in the apex of the left lower lobe; on the right side was a 2 cm. diameter rounded shadow in the upper lobe.

Her X-ray on admission, some ten months later, showed an opacity in the left upper lobe continuous with the hilum, which was increasing in size. The shadow in the right upper lobe was unchanged. Bronchoscopy was uninformative. It was considered that she had a primary neoplasm of the left upper lobe and thoracotomy was advised.

At operation (R.B., 19.5.58), left thoracotomy disclosed a hard mass in the upper lobe at the hilum. A large cavity was palpable in the apex of the lower lobe. Left pneumonectomy was considered to be the procedure of choice and was performed.

The pulmonary artery was dissected out. It was found to be quite solid to within 1 cm. of its origin. It was transected immediately distal to this, after which a plug of growth was expelled from the proximal end, which was then secured and ligated. Dissection pneumonectomy was completed, with removal of a few enlarged hilar lymph nodes.

Her post-operative course was uneventful and when last seen, some ten months later, she was quite well. The shadow in the right upper lobe remained unchanged.

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Pathology Report on Resected Specimen—Left Lung and Glands

The specimen consists of a left lung. The upper lobe contains a well-defined lobulated white fleshy tumour, 10 cm. in maximum extent, reaching outwards from the hilar region almost to the medial, anterior and lateral surfaces, but with little involvement of the apical part. The pulmonary artery is filled with similar growth, 1¾ cm. in diameter, extending to the cut end. A hilar lymph node just below the artery is involved by direct extension from the main mass. Two other lymph nodes show caseous areas.

Towards the apex of the lower lobe there is an irregular cavity about 1½ cm. in maximum extent with induration of the surrounding tissue.

Sections of the growth show it to be a fairly anaplastic sarcoma with no indication of the precise tissue of origin. Tumour giant cells and mitoses are quite frequent. There is some fibre formation in parts, with scanty collagenisation which may be partly an X-ray reaction. Whilst the edge of the tumour is fairly well defined and apparently encapsulated in places, there is also evidence of infiltration at the periphery.

Section of the pulmonary artery shows it to be filled with similar sarcomatous growth. The arterial wall is invaded in places.

Section of the cavity in the apex of the lower lobe shows it to be tuberculous. It is lined by tuberculous granulation tissue and there are tubercle follicles in the adjacent lung.

Sections of seven lymph nodes show direct invasion of one by growth, but there is no evidence of metastases in the others. Two contain caseating tuberculous areas and two others contain an occasional tubercle follicle.

CASE 2. A man aged 45 was admitted to the London Chest Hospital in October 1958 with a three-month history of a productive cough and effort dyspnœa following a pyrexial illness. He had had one episode of hæmoptysis in September.

X-ray (Fig. 1) showed an opacity in the left upper lobe anterior segment, with what appeared to be a cavity adjacent to it. The vascular shadows at the left hilum appeared denser than those on the right—it was only in retrospect that the absence of peripheral vascular markings in the left lung was noted.

Bronchoscopy, bronchography and sputum examinations were negative. As the peripheral shadow in the left upper lobe was enlarging on comparison with a pre-admission film, thoracotomy was advised.

Operation was performed by Mr. J. R. Belcher. The mass in the upper lobe felt hard. The lower lobe was normal; there was no significant lymphadenopathy.

Upper lobectomy was embarked upon. The pulmonary artery was dissected out and found to be solid to palpation, almost to the pulmonary trunk. Upper lobe branches were displayed and found to be similarly involved.

The condition was deemed inoperable owing to the extent of proximal involvement of the artery. A segment of one of the upper lobe branches was removed between ligatures for purposes of histology. Growth could be seen exuding from each cut end. The chest was closed.

The patient's post-operative condition being satisfactory, an angiocardiogram was performed three weeks after operation. The purpose of this investigation was to determine the extent of the intra-arterial pulmonary involvement, particularly of the contralateral lung, prior to considering radiotherapy. Surprisingly, in addition to a failure of the left pulmonary artery to fill, this

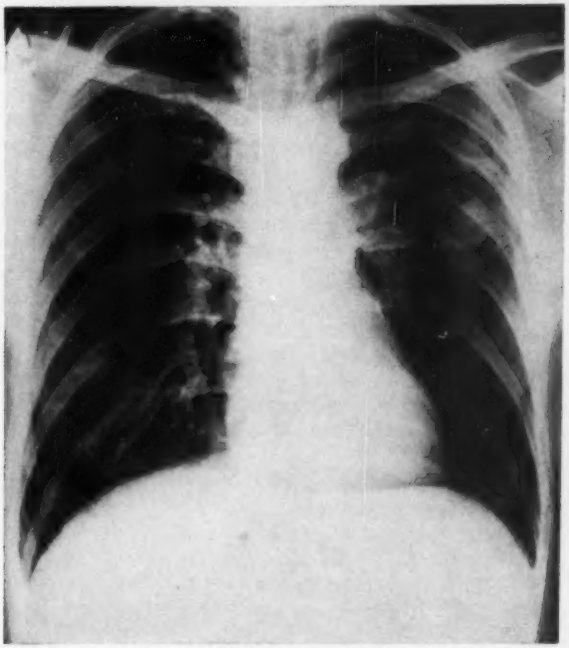

FIG. 1.—Case 2. Note absence of pulmonary vascular markings on left.

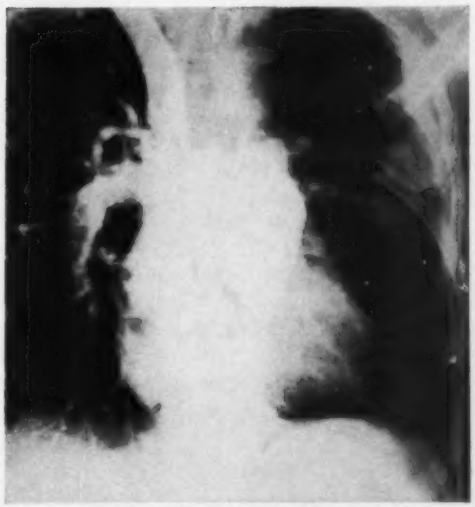

FIG. 2.—Case 2. Angiocardiogram showing complete failure of left pulmonary artery to fill, and filling defect in right ventricle.

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showed a large filling defect in the right ventricle (Fig. 2), almost certainly due to an intracardiac tumour.

Pathology Report on Resected Specimen (Fig. 4)

(1) *Biopsy from Sub-pleural Tumour of Apical Region of Left Lower Lobe.*

(2) *Biopsy from Tumour of Lingular Artery.* 30.10.58.

(1) Specimen consists of a biopsy of sub-pleural tumour in apical region of Left Lower Lobe, measuring 1×0·7×0·6 cm. It is homogeneously white and translucent.

Histology. This material consists of pleomorphic cells in a myxomatous stroma.
There are scanty mitoses and tumour giant cells.

(2) Specimen consists of a biopsy of the lingular artery, measuring 0·7×0·4×0·4 cm.
Vessel lumen is not distinguished.

Histology. The biopsy is composed of a cellular tumour which appears to be infiltrating the vessel wall. The tumour cells resemble those from the biopsy of the lung but the stroma is not myxomatous.

Summary. Both biopsies show a connective tissue tumour which is probably malignant.
The lingular artery biopsy is more cellular than the biopsy on the lung tumour which shows myxomatous features.

Discussion

Both these cases exhibited the common feature of a sarcoma completely filling one pulmonary artery and extending along its branches. In this respect they resemble the eight previously reported cases.

It was interesting to re-examine our patients' X-rays in the light of the knowledge gained at thoracotomy. In both the lack of peripheral vascular markings on the affected side was quite obvious. The hilar vascular markings, on the other hand, were of increased density. We feel that this should have been noted and, had we been sufficiently aware of the condition, it could have been a major factor in arriving at a diagnosis.

The other interesting finding was a presumed right-sided intracardiac tumour in Case 2. It corresponds with the case reported by Pritchard, as discussed above. The tumour in his case was a myxosarcoma; myxoma is the most common intracardiac tumour, and not infrequently shows sarcomatous changes. We feel that it is quite possible that at least some of the previously reported cases of solid sarcomatous artery follow a primary tumour in the right heart. We have been unable to obtain an angiocardiogram in Case 1.

Summary

Two further cases of the solid sarcomatous pulmonary artery are described. One was resectable by pneumonectomy. The significance of peripheral vascular markings disappearing from the lung field in both cases is emphasised.

The second case was found on angiocardiography to have a filling defect in the right ventricle. We suggest that this was the primary tumour, metastasising to the pulmonary artery. It is also possible that in some of the other reported cases a similar ætiology obtains.

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EOSINOPHILIC GRANULOMA OF BONE

By John M. Reid

From the Thoracic Unit, Mearnskirk Hospital, Glasgow

Introductory

Eosinophilic granuloma of bone has gained increasing prominence in the literature in the past few decades, though there is still a wide divergence of opinion as to its exact ætiology.

Possibly the condition was first recorded in 1865 by Thomas Smith, although its significance remained extremely dubious until comparatively recent times. The first reference to eosinophilic granuloma in British literature was by Fraser (1935), and although further reports appeared (Hill, 1949; Nesbitt, 1955; Lightwood, 1955; and Wilkinson, 1956) most articles on the subject have emanated from the U.S.A. (Otani and Ehrlich, 1940; Farber, 1941; Mallory, 1942; Michael and Norcross, 1945; Cox, 1946; Thannhauser, 1947; and Compere *et al.*, 1954) or the Continent (Kyrkland, 1926; Mignon, 1930; Schairer, 1938; Henschen, 1943; Holm, Teilum and Christensen, 1944.)

The object of the present paper is primarily to record a further case of eosinophilic granuloma occurring in this country, and also to discuss the varied views as to ætiology and therapy.

Case History

The patient, a male aged 17 years, was admitted to a Medical Ward in Mearnskirk Hospital in April 1959. He came of healthy parents and had been perfectly well until his present complaint. Two months prior to admission he had developed a stabbing pain in the left scapular region. The pain persisted, though of diminished severity, and he was referred to his appropriate Chest Clinic, where he was found to have a swelling of the sixth left rib posteriorly. He was admitted to hospital for further investigation.

Clinical examination was essentially negative, apart from the presence of a slightly tender swelling over the sixth left rib posteriorly, medial to the vertebral border of the left scapula. The swelling was not fluctuant and was firmly adherent to the underlying rib. No other palpable bony abnormalities were present, and there was neither lymphadenopathy nor hepato-splenomegaly.

Chest X-ray (Fig. 1) showed normal lung fields, but the sixth left rib close to its angle showed a circumscribed oval translucent area of osteoporosis with localised bulging of the periosteum. The radiologist's report suggested the possibility of malignancy, either in the nature of a sarcoma or chondro-sarcoma.

Biochemistry

Ser. Cholesterol was 186 mg. %, blood urea 19 mg. %. The Ser. Pot. was 19·5 mg. % (5 mEq./L.), whole blood Pot. 188 mg. %, red cell Pot. 379 mg. %. The Serum Sod. was 325 mg. % (141·2 mEq./L.), chloride 621 mg. % (106·2 mEq./L.) The plasma CO_2 was 42·8 mg. % (19·1 mEq./L.), and the P.C.V. was 47 ml. %.

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Plasma proteins as determined by the method of Biuret were 8·4 G. % (A : G ratio was 0·83 : 1.) The electrophoretic pattern was normal; alpha 1 glob. fraction was 0·56, alpha$_2$ glob. 1·09, beta$_2$ glob. 0·84, gamma glob. 2·1. E.S.R. (Westergren) was 12 mm. in 1 hour. The hæmoglobin was 13·5 G. %, and the W.B.C. 9,200/c. mm. Differential W.B.C. showed neutrophils 68%, lymphocytes 24%, monocytes 4%, eosinophils 3%, basophils 1%. The eosinophil count was 194/c. mm. The Bence-Jones test (Bradshaw) on his urine proved negative.

In view of the radiological appearances it was decided to resect the affected portion of rib, and this was carried out on 24.4.59. The post-operative course was uneventful. Fig. 2 shows the post-operative X-ray. Histology of the resected specimen was reported as follows: "The lesion is completely surrounded by a band of fibrous tissue of varying width lying within the bone tissue proper of the rib. The cyst content is highly cellular, and the cells are set in amorphous eosinophilic material in which run fine strands of fibrous tissue. Most of the cells are of the eosinophil series, their characteristic large, coarse granules can be seen in routinely stained sections, but they have been selectively picked out by special techniques. Many have a rounded nucleus, suggesting that they are at the myelocyte stage of development, but a few typical multi-lobed forms also appear." (Figs. 3 and 4.)

On receipt of this report radiological examination of the entire skeleton was performed. Although the long bones were completely normal, skull X-rays showed the typical "geographical" outline suggestive of the coalescence of multiple smaller lesions (Figs. 5 and 6).

Discussion

It was Fraser in 1935 who first postulated the relationship of eosinophilic granuloma of bone to Niemann Pick's Disease, Gaucher's Splenomegaly, Tay-Sachs Disease, Letterer Siwe Disease, and Hand-Schuller-Christian Disease. He grouped these conditions in the category of lipoid granulomatosis.

Geschicter and Copeland (1949) suggested the following classification:

LIPOID GRANULOMATOSIS AND RETICULO-ENDOTHELIOSIS OF BONE

Lipoid granulomata	*Non-lipoid granulomata*	*Reticulo-endotheliomata*
Xanthomatosis with cholesterolæmia (symptomatic and primary types)	H.S.-Christian Disease	Reticulo-endotheliosis, benign and malignant
Niemann Pick's Disease	Eosinophilic granuloma of bone	
	Boeck's Sarcoid	

Marshall and Perry (1952) also acknowledged the affinity of eosinophilic granuloma to the lipoidoses, and described a patient who had had a pathological fracture of his femur due to an eosinophilic granuloma ten years previously, and subsequently developed H.S.-Christian Disease with associated diabetes insipidus.

Hill (1949), describing a case occurring in a 15-year-old boy, gave a very concise and full review of the literature up to that period. He mentioned that up to 1948 a total of 72 cases of eosinophilic granuloma had been recorded, including 9 by Hamilton *et al.* (1946) and 5 by Dundon *et al.* (1946).

The condition tends to affect particularly children and adolescents, with males predominating. Most frequently it occurs as a solitary lesion, involving

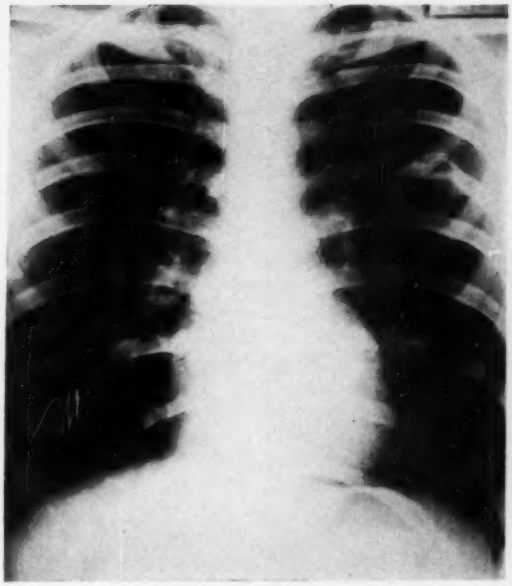

FIG. 1.—Pre-operative chest X-ray showing an oval translucent area of osteoporosis of the 6th left rib.

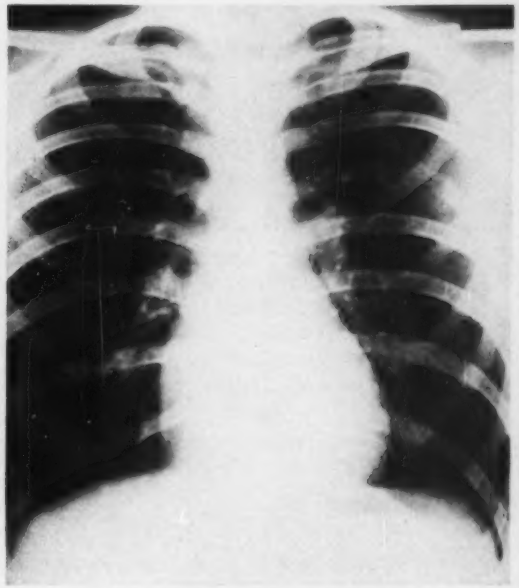

FIG. 2.—Post-operative chest X-ray showing resected portion of 6th left rib.

FIG. 3.—A low-power view of the specimen showing the lesion to be completely surrounded by a band of fibrous tissue. The cyst content itself is highly cellular.

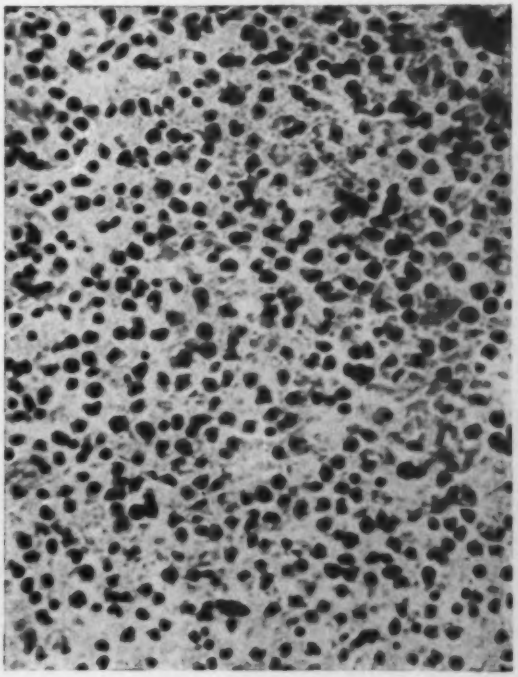

FIG. 4.—A high-power view of the lesion showing the highly cellular content of the cyst—most of the cells of the eosinophile series.

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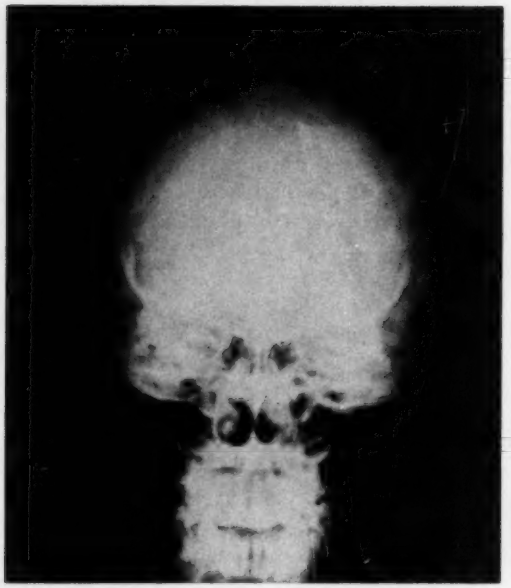

FIG. 5.—P.A. view of skull, showing multiple small foci.

FIG. 6.—Right lateral view of same.

FIG. 7.—Left lateral view of the same.

in particular the membranous bones, but in nearly one-third of the cases recorded there have been multiple lesions. Green and Farber (1942) mentioned the occurrence of twenty-five lesions in their case. The skull is the site most commonly involved, both in solitary and multiple foci, with the rib, femur and vertebræ next, in that order.

The clinical features vary according to the site. A solitary lesion usually presents simply as a localised swelling with or without pain, though severe malnutrition may ensue in cases with multiple lesions. Diabetes insipidus may be present when the skull is involved, and the condition then virtually merges into that of Hand-Schuller-Christian Disease.

In the present case the presenting symptom was a swelling over the sixth left rib, and although radiological examination revealed diffuse involvement of the skull too, there were no associated symptoms in the form of headache, cranial nerve palsy or diabetes insipidus. Biochemically there was no disturbance of the plasma proteins, electrophoretic pattern, nor serum cholesterol. This is in accord with previous reports of eosinophilic granuloma, thus differing from the other xanthomatoses where the serum cholesterol is usually raised.

Radiologically the lesion appears as an oval or circular area of translucence arising in the marrow with elevation of the surrounding cortex. It may simulate osteomyelitis, osteoclastoma, Ewing's tumour of bone, myeloma (solitary and diffuse), osteogenic sarcoma, and in diffuse lesions osteitis fibrosa cystica and multiple osseous metastases. Osteitis fibrosa cystica can be distinguished by the appropriate biochemical features, as can myelomatosis. However, in most cases the diagnosis is established by histological examination either of the resected lesion or of the aspirated material.

Pathology

The pathological picture consists of a cystic area, usually arising in the marrow. This cystic area is occupied by soft, brownish granulation tissue which may be streaked with yellow necrotic material, and there may be supernatant clear fluid present in the softer lesions. Histologically there are sheet-like collections of large phagocytic cells of the histiocyte type, interspersed with numerous eosinophil leucocytes. Multinuclear giant cells are especially frequent in the areas of hæmorrhage and necrosis. The characteristic component is a large mononuclear cell derived from the reticulum cell of the marrow.

Holm, Teilum and Christensen (1944) divided the pathology into four separate phases: (1) proliferative, with histiocytes and eosinophils; (2) granulomatous, with increase in blood vessels, fibrils and reticular cells; (3) xanthomatous, with cell nests and isolated foam cells; (4) fibrous, which may be regarded as the stage of healing.

Ætiology

Fraser's work on this aspect has already been referred to. He concluded that the condition originated as a local tissue reaction to hypercholesterolæmia.

Jaffe and Lichtenstein (1940), while recognising that all the xanthomatoses,

including eosinophilic granuloma, were different expressions of the same basic disorder, postulated that the process represented a distinctive inflammatory reaction to some as yet undetermined infective agent. In eosinophilic granuloma there is no hypercholesterolæmia, and the characteristic lesion develops only in the skeleton, in one or more bones. Abundant eosinophils with histiocytes comprise the histological picture, and there is no tendency to collagenisation nor deposition of lipoid material. The prognosis is excellent in most instances, and cure follows either simple curettage or surgical excision. The condition may even regress spontaneously without any therapy. However, occasionally lipoid deposition may occur eventually, and the condition then assumes the characteristics of Hand-Schuller-Christian Disease with hypercholesterolæmia and the triad of calcarious osseous defects, exophthalmos and polyuria, as in the case referred to by Perry and Marshall.

The patient under discussion possibly falls into this transitional phase. While at present exophthalmos and polyuria are not present and the serum cholesterol is not raised, he has very definite calcarial osseous defects. At some future unspecified date he may well develop diabetes insipidus. The decision whether to irradiate the skull deposits at present when the patient is asymptomatic may be controversial. Fripp (1958) favours irradiation prophylactically in an attempt to prevent the emergence of overt diabetes insipidus.

Our knowledge of the precise function of eosinophil leucocytes is still incomplete. Their presence is indicative of reaction to certain abnormal stimuli, be they in the nature of allergens (as in bronchial asthma), parasitic infestations (as in ascariasis with pulmonary manifestations), or locally as in such granulomatous conditions as under discussion. Hill (1949) suggests that injury may be a precursor to eosinophilic infiltration in solitary lesions, the injury causing the liberation of some toxic substance which initiates the reaction. Obviously this theory could not be applicable where there were multiple foci.

An interesting report by Compere *et al.* (1954) suggested that the condition of osteochondritis affecting the spine (Calve's Disease or vertebra plana) is in fact a variant of eosinophilic granuloma. Biopsy was carried out in 4 cases of Calve's Disease, and the typical histological picture of eosinophilic granuloma was found. Irradiation resulted in complete cure.

Prognosis and Treatment

In simple, uncomplicated eosinophilic granuloma the prognosis is excellent. Complete cure usually follows either simple aspiration or surgical excision, or even occurs spontaneously at times. Where the condition is assuming the characteristics of Hand-Schuller-Christian Disease the outlook becomes less favourable.

Summary and Conclusions

The relevant literature of eosinophilic granuloma is reviewed. A further case is described, involving one rib with multiple foci in the skull. The former was treated by excision, while treatment of the calcarious deposits is still under discussion.

The ætiology is discussed, and the relation to the xanthomatoses as first mentioned by Fraser is noted. Previous writers have suggested a local inflammatory reaction to some toxin or injury as possible causal factors.

In cases of eosinophilic granuloma with multiple foci there is a fine dividing line from Hand-Schuller-Christian Disease. While solitary lesions can be treated successfully by simple excision or aspiration, irradiation is required for multiple foci.

The author wishes to thank Dr. S. Kennedy, under whose care the patient was admitted, for permission to publish. It is a pleasure to record the help afforded by Mr. R. S. Barclay and Mr. T. M. Welsh, who operated on the patient, and to Drs. Craik and Barrie of the Victoria Infirmary, Glasgow, who reported the histological findings. Mr. Gray, Clinical Photographer, reproduced the plates.

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CHEST DISEASES IN BIBLICAL TIMES

By Eric R. Smith*

From the Stockport Chest Clinic

In dealing with the very early history of chest disease, the most convenient and perhaps the most attractive period is probably from Genesis to Revelation —in other words, from the dawn of recorded history when ignorance and superstition went hand in hand, to the days of the awakening of scientific medical knowledge, and as this period coincides with the period covered by the Bible it is perhaps possible to weave a thoraco-Biblical story out of the scattered threads of evidence available, confined roughly to the geographical districts familiar to the reader of the Holy Bible.

My story begins just over 4,000 years ago in the land between the Tigris and Euphrates, and the Arabian desert on one side and Persia on the other.

Here it was that a great civilisation known at first as Sumerian and later as Babylonian and Assyrian had arisen, probably some 1,500 years earlier.

Because of its climate it was a veritable hotbed of broncho-pulmonary disease, which seemed more common than other diseases. Here it was that we find one of the earliest authentic references to tuberculosis—in the code of its King Hammurabi around the year 2200 B.C., and there is an ancient Babylonian invocation against consumption.

While Hammurabi was on the throne there lived in the capital city a man named Terah who had three sons of whom the second, named Haran, died before his father, Terah, in his native land in Ur of the Chaldees. Terah then took his third son, Abram, and his grandson, Lot, along with their respective wives and went forth with them to go into the land of Canaan.

In these days in Sumeria health was considered a great blessing and the position of a sick man in society was aggravated by the view that illness was a punishment for sin—a view that was transmitted to Judaism and may have had some influence on the writings of the Pentateuch many centuries later.

Considering this, is it not reasonable to assume that Haran had died from some chest trouble and that Terah suggested to his family they should find a healthier place to live in?

It is on record that even at this early date there was an exchange of physicians between Egypt and Assyria and it is more than likely, therefore, that Terah and Abraham had heard of the comparatively perfect climate of Egypt and of the Egyptian boast that they were the healthiest of all mortals.

There must have been something about Egypt that appealed very strongly to Abraham to induce him to spurn the land of Canaan which the Lord had promised him, and it would appear that the famine he encountered in the south could not have been very severe, as he returned to that same place after being banished from Egypt by Pharaoh only a few months later.

* Abridged from Presidential Address to the North West Thoracic Society.

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There is no evidence that chest disease constituted any grave problem in Egypt at this time, nor that tuberculosis existed in any form, and I have not been able to discover any reference to non-tuberculous chest disease prior to the publication of the first papyrus in 1600 B.C.

It was 200 years after Abraham that the first known case of tuberculosis occurred in Egypt and that took the form of Pott's disease, followed by an increasing number of similar cases over the next thousand years or so, the best example being a priest of Ammon who died about 1000 B.C., and who had several vertebræ affected, together with a large psoas abscess.

The Abraham period coincides roughly with the pyramid age of Egypt, a period of great art and endeavour, and yet it is amazing that the Egyptians of this age, who had eviscerated numberless bodies in the process of embalming—it is estimated that some 10 million bodies were embalmed in Ancient Egypt—when opening a chest had no idea what they were looking at, had no idea of respiratory physiology and practically no knowledge of anatomical detail. They even considered the ears and the anus to be organs of respiration, and held that the breath of life entered the body through the right ear and the breath of death through the left.

It is on record that the Pharaohs of this time had specialist physicians for most parts of the body—hair, teeth, eyes, skin, bones, etc.—and a physician was even appointed for the Royal Anus, but there is no mention of a specialist for the lungs or chest. Probably the real answer is that because there was so little chest disease to treat there was no need for a chest physician.

But gradually things changed, Egyptians became wiser and more concerned as they became more susceptible to chest diseases, and in 1600 B.C. we begin to see a glimpse of clinical appreciation.

In that year the Ebers and Edwin Smith papyri were written and from these it would seem that an attempt was now being made by the Egyptian physicians to approach their medical problems in a somewhat more scientific manner, although superstition was still much in evidence, but from their attempts to describe symptoms and signs, and from the type of treatment they meted out, we can form a fair idea of the kind of diseases from which they now suffered.

In the Edwin Smith papyrus we have the first description ever of a chest wall abscess—here is a verbatim translation:

" The clamminess of the surface was encountered and palpation revealed a very large swelling protruding on his breast—oily like fluid under the hand." I would emphasise that the text speaks of *his* breast and not hers and hence the abscess was in all probability not mammary but either a cold abscess or even a pointing empyema. The same papyrus describes the fluctuating cystic swelling as " one that comes and goes under thy fingers."

The Ebers papyrus contains what is almost certainly the original note on *Angina Pectoris*—" The patient has pain in his arm, in his breast, and in one side of his cardia, and it is death that threatens him."

The chapter headed " The Physician's Secret. Knowledge of the heart's movement, knowledge of the heart " goes on to describe how the vessels go

from the heart to every limb, and by feeling the pulse you feel the heart that speaks out of the vessels of every limb.

It then proceeds to enumerate 46 of these vessels, allotting 4 to the ears—2 to the right and 2 to the left—the breath of life still entering by the right ear and the breath of death by the left. There are 4 vessels to the lung and to the spleen—it is they which give to it humor and air—and there are 4 vessels to the anus and it is they which cause humor and air to be produced for it.

It seems our physician cannot get away from the old idea of the relative importance of the lungs and anus, though he has by now granted them an equal blood supply.

Halitosis and offensive sputum are referred to in the Ebers papyrus, which states that phlegm putrefies when it does not descend to the sacral region.

Incense burning in the temples probably originated as a part of the ritual in idol worship, and soon its use was appreciated as a deodorant to cope with the body odours of the crowds of worshippers. Later still it came to be used in the treatment of these foul breath cases, and then extended to the general treatment of broncho-pulmonary disease—probably when other remedies had failed, and partly because of the success of certain resinous materials after trial and error. Frankincense, myrrh, storax and benzoin, laudanum and turpentine, also earned honourable mention. Some 1,800 years later Galen was still advocating inhalations of frankincense for hæmoptysis, comparable to the benzoin prescribed in a steam kettle for bronchitis.

By this time Egyptian medicine must have exerted considerable influence beyond the borders of its own country. Physicians were exchanged with the courts of Syria and Assyria and we find in Assyria and Egypt a similarity of approach to disease in general, but a striking difference in the stress placed on chest disease in Assyria, thus adding weight to my original statement about the prevalence of chest disease here.

Most of our knowledge of early Assyrian medicine is derived from the huge collection of clay tablets discovered in the library of Ashurbanipal. In them are found descriptions of such symptoms as cough, sputum, chest pains, even hæmoptysis, and certain texts which undoubtedly refer to pleural and broncho-pulmonary pain, dyspnœa and even suggestions of pneumonia.

In Egypt lungs were under the care of the God Min. In contrast, the Babylonians believed that diseases were brought about by evil spirits, and that Mergal, the God of Pestilence, had fourteen attendants who infested mankind with febrile illnesses—Ashakku caused fever and consumption and Suala diseases of the chest.

But they had similar anatomical ideas—the Babylonian anus, like the Egyptian, was still an organ of respiration and its importance in treatment was stressed. One prescription runs as follows: " If a man is affected in the lungs, thou shalt spread powder of tar over a thorn fire, let the smoke enter his anus, his mouth and his nostrils, it shall make him cough." On the other hand, some of their treatments had a more modern flavour, and the linseed poultice was introduced.

It was probably the Hindus who at this time introduced an extensive pharmacopœia to Assyria and it is interesting to note that liquorice, myrrh, squills, vinegar of squills, pine tar, turpentine, laudanum and honey were introduced to the world at this period, and stood the test of time as popular medicaments in the treatment of chest diseases until long after my own student days were over.

In any case, they had implicit faith in their methods of treatment, as almost all the remedies described in Ashurbanipal's collection concluded with the words, " Do this and he shall recover."

Two centuries later in Egypt the young Pharaoh Amenhotep IV was on the throne. He died at the early age of 28—a mural depicting him with his wife Nefertiti and their three children, enjoying a sun bath, can be seen. It has been suggested that the children are being treated for rickets, but, judging from the appearance of all five, they seem rather to be suffering from Schachefess or the wasting disease, which had begun to show itself amongst the Egyptians.

I suggest as a working hypothesis that Amenhotep, or Ikhnaton, as he was then known, had tuberculosis and that his disease was hyper-activated by over-exposure to direct sunshine after he had adopted his new religion of Solar Monotheism.

One of the children married the Pharaoh Tutenkhamon, who also died very young, possibly having been infected by his father-in-law, and it is perhaps a noteworthy coincidence that within fifty years of the death of Tutenkhamon the Hindus had begun to realise the danger of marrying into a tuberculous family and had also begun to fear that the disease might be transmitted from parent to child.

Manu, the Hindu Noah, wrote his book of laws at this time, 1300 B.C., and in these he stated that a consumptive was unclean, and a Brahman was forbidden to marry a consumptive nor must he marry a girl whose ancestors had been consumptive.

And now with tuberculosis recognised as a menace in India, with tuberculosis and non-tuberculous chest conditions causing as much concern as ever in Assyria and Babylon, and with tuberculous spines and wasting disease taking its toll of the Egyptians, we enter the famous 19th Dynasty of Egypt, a period of great importance for its early public health laws, and its joint application of religion and medicine to conduct.

It is obvious from the outset that Moses had four great objectives:

First, to terminate the enslavement of the Israelites. *Secondly*, to keep them faithful to Jehovah. *Thirdly*, to maintain internal peace amongst them, and *fourthly*, to preserve their health through his and future generations.

We may ask what relationship there is between the Mosaic Code and chest disease and what we can pick out of it to suit our purpose.

Tuberculosis had been spreading throughout the East and had also been found in cattle and other domestic animals. The Hebrews were the first people to proscribe the eating of the flesh of a tuberculous animal and even of some animals likely to suffer from tuberculosis.

I think I am right in stating that Moses laid down the law that at the slaughter of an animal for human consumption the officiating priest, on opening the thorax, passed his hand over the whole extent of the pleural surfaces, and if his hand were held up by adhesions the animal was condemned forthwith. In the Talmud, however, this rule had been altered a little and by the end of the B.C. era simple pleural adhesions were pardonable, but not pleural calcification, broncho-pleural fistula, multiple lung abscesses or cavities, which rendered the carcass completely unwholesome.

The hunchback held much the same position in the aristocratic Egyptian household as the jester in mediæval English history, but Moses must have recognised the hunchback as a tuberculous subject, for he forbade him to enter into the Inner Sanctuary or to come within the precincts of the high altar.

The Hebrews were warned not to touch the dead or to come into unnecessary contact with a sick person, and if such contact had taken place, had to undergo a period of atonement and cleansing.

The Pentateuch sets out clearly the sanctions against those who disregarded the anti-tuberculosis rules. For example—

Deut. 28, *v.* 15/22. " If thou will not hearken unto the Lord thy God, to observe to do all his commandments and his statutes which I command thee this day,—then the Lord shall smite thee with a consumption, and with a fever, with an inflammation and with an extreme burning and they shall pursue thee until thou perish." (Rashi's translation.)

Or in Leviticus 26, v. 15/16.

" If ye despise my statutes or if your soul abhors my judgment and ye break my covenant, I will appoint over you terror and consumption that shall cause sorrow of heart and ye shall sow your seed in vain."

Coronary and aortic disease take pride of place in the diseases of this time. The Ebers papyrus describes anginal pain and Rashi interprets Deut. 28, v. 66 thus:

" In strange lands you will be troubled with a palpitating heart and a sense of impending death—agonising pains and a tortured soul,—your life will hang in the balance and you will dread the day and night. In the morning you will say—' Would God it were evening ', and in the evening you will say—' Would God it were morning ', you will be oppressed by the fear of your heart."

The Ebers papyrus twice makes mention of *Aneurysm*, but does not precisely specify aortic.

Bronchiectatic abscesses occurred when the phlegm putrefied on failing to descend to the sacral region.

Pneumoconiosis has been recognised by Ruffer as occurring in a priest of the 20th Dynasty—and the same author describes another mummy of the same period showing unmistakable signs of pneumonia in the stage of grey hepatisation.

Pleurisy was probably fairly common and signs of pleural adhesions have been found in several mummies by Elliot Smith, Dawson and Wood Jones.

For the first account of resuscitation and the first major thoracic operation I would refer you to Genesis 2, v. 7—" And the Lord God created man out

of the dust of the ground and breathed into his nostrils the breath of life and man became a living soul," thus originating the idea of mouth-to-mouth resuscitation and artificial respiration.

At about the same time as this primitive version of Genesis was being written—about 850 B.C.—Elijah practised artificial respiration on the son of the widow of Zarephath, and his successor, Elisha, copied more exactly the method described in the Biblical version of the creation.

" And Elisha came into the house and behold the child was dead and laid upon his bed. And he went up and lay upon the child and put his mouth upon his mouth and stretched himself upon him again and the child sneezed seven times and opened his eyes " (2 Kings 4).

The story of the creation of Eve has special interest to the thoracic surgeon, in that in a most imaginative way it describes a major surgical operation under general anæsthesia.

" And the Lord God caused a deep sleep to fall upon Adam and he slept, and he took one of his ribs and closed the flesh instead thereof and the rib made he woman."

Rashi, writing in the twelfth century of the Christian era, quotes the Midrash Rabbi: " So God created man in his own image, in the image of God created he him—male and female created he them," and describes the progenitor of the human race, Adam, as composed of two forms, male and female, joined together by their chests as Siamese twins and later divided by means of an operation.

At about this same time Homer gave in his Odyssey news of the invasion of Greece by the tubercle bacillus. He refers to a father—presumably his own—who lies in sickness and is a long time wasting away: " Nor did any disease come upon me such as by grievous consumption takes the soul from the body."

By the time of Hippocrates tuberculosis was very prevalent and the disease was obviously very much in the minds of both medical and non-medical writers.

Stimulated by Alcmæon and fostered by Hippocrates and his colleagues at Cos, they came to manifest a keen observation of the symptoms of chest disease in general and of the causes, symptoms, developments and prognosis of tuberculosis in particular; and it is more than likely that some of their physicians had a visual acquaintance with both the nodular and the cavitating forms of the disease.

Alcmæon—a pupil of Pythagoras—around 500 B.C. began in Greece the scientific dissection of animals and first described the Eustachian tubes, and yet preserved some flavour of Egypt when he enunciated the theory that goats breathe through their ears.

Erasistratus followed up the practice of anatomical dissection some 200 years later by human vivisection, dissecting criminals procured from the prisons by Royal permission. He expounded the theory that the air enters the lungs and then the heart, where it is changed into the vital spirit and then carried throughout the body by the arteries.

If, then, this was still the extent of the knowledge of anatomy and physiology

of chests 300 years before Christ, how much more should we marvel at the development of clinical sense of those members of the school of Cos who, working in comparative ignorance of what went on inside a normal chest and possessing neither thermometers nor stethoscopes, yet whose ideas, methods and procedures, whose accuracy of clinical observation and unremitting care in case taking, have ever been and still are a source of inspiration to all medical men?

Euryphon, who practised in Cnidos when Hippocrates was a boy, gives in his *Cnidiæ Sententiæ* a lucid if somewhat elementary account of phthisis which he was treating with cautery, a milk diet, and above all with rest and quiet.

And while Hippocrates was still in his youth, Herodotus was describing hæmoptysis as a cause of consumption.

Hippocrates described phthisis in the first and second books of his *de Morbis* and noted the frequent association of tuberculosis with other complications of pneumonic disease, and, although he failed to differentiate between tuberculous and non-tuberculous empyema, he consolidated the foundation of a new approach to chest disease.

Dealing with tuberculosis, he says that—" Of all diseases that raged on the island of Thasos, none reaped such a bountiful harvest as consumption; of all maladies it was the most virulent and the most difficult to treat and exacted the most deaths."

He then proceeds to enumerate the symptoms—languor, physical debility, cough, thick yellow sputum, frequent chills, continuous fever, excessive perspiration, marked emaciation, dullness, and hoarseness of the voice, bent finger nails, redness of the cheeks, hæmoptysis, swelling of the feet and disorder of the bowels, and usually occurring between the ages of 18 and 35 years.

He also noted the presence of phymata or nodules in the lungs, and observed that people dying with spinal curvature usually have hard and unconnected tubercles in the lungs.

Perhaps Hippocrates had been struck with the passage, " I will visit the sins of the fathers upon the children," for although he spurned the idea of sickness being a punishment for sin, he firmly believed in the hereditary transmission of tuberculosis, for " Consumptives beget Consumptives."

I wonder how many doctors today give their patients a good shaking and listen for splashing sounds when suspecting a hydropneumothorax, and when listening to pleural friction sounds remember that Hippocrates first described these—which, incidentally, he heard by putting his ear to the chest wall—as the sound of creaking leather. Again, the presence of clubbed fingers in chronic chest cases was first described by Hippocrates, in addition to pleuritis, empyema, broncho-pleural fistula and orthopnœa; and he first noted the importance of nummular sputum and the presence of mucoid pellets in the sputum of asthma patients.

Nevertheless, Hippocrates had his critics, notably Isocrates, who favoured the contagious rather than the hereditary theory of the ætiology of tuberculosis.

His colleague, Aristotle, undoubtedly the greatest biologist of the Greeks, also stressed the dangers of contact.

There are many other examples, but space permits only reference to Aretæus, who gave an even more clear and definite description of phthisis than Hippocrates, drawing the distinction between true phthisis and empyema, and was probably the first to recognise tuberculous cavities as such, and tuberculosis in children.

Nor should we neglect to mention Rufus, who advocated open drainage in cases of empyema, for he says: " This allowed the pus to drain out and the ulcer to absorb."

By A.D. 100 and at the close of the Biblical period the early Christians were unsympathetic towards orthodox medicine as, becoming obsessed by the miracles of Christ, they considered the work of physicians to be directly opposed to their ideas of spiritual healing.

This paper has traced a long journey from the Ganges valley through Assyria and Babylon to Palestine and Egypt, and back again through Palestine to Greece and Rome, seeing knowledge of chest disease developing and spreading along the lines of the journey—how each country and race in turn came under its shadows, with the exception of the faithful children of Israel. *There is no reference in the Bible or in fact in any other literature of this period to any case of tuberculosis amongst the Hebrews*—and, what is still more significant, *there was no word for cough in the ancient Hebrew language.*

Was this in accordance with the prophecy of Zechariah, who threatened the despoilers of Jerusalem with a plague but added that the sons of Jacob should not be consumed? And is it then so that the faithful Jew who hearkened to the voice of the Lord his God and kept his commands and his statutes earned for himself the epitaph " Nec Tamen Consumebatur "?

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A CASE-FINDING TUBERCULOSIS SURVEY IN SINGAPORE, 1958

By Cotter Harvey and C. Rubinstein (*Sydney, Australia*) and C. E. Smith (*Singapore*)

Introductory

The State of Singapore, with a total area of 224 square miles, has a humid and enervating climate, an irregular but frequent rainfall of some 70 inches per annum, and a remarkable absence of wind, except for the tropical storms or "Sumatras."

At the time of the Census of 1957 the population was 1,445,930, 1,040,570 of whom were Chinese, 197,067 Malaysians and 124,083 Indians and Pakistanis, and over half the population was under the age of 19. In the City area of 31 square miles reside over one million people. The birth rate is one of the highest in the world with resultant overcrowding and employment problems.

The basic and traditional commercial and residential unit is the shop house, a two- or three-storey terrace building with narrow frontage and great depth. Original rooms are partitioned into many, often windowless, cubicles which could contain a family of six to eight people. Under these circumstances a considerable resistance to tuberculosis must have been built up by the population in order to ensure survival at all.

Singapore has efficient Medical and Health Services, but they find it difficult to cope adequately with the rapidly increasing population.

The high prevalence of tuberculosis in Singapore has been recognised for many years as a serious public health problem, with morbidity between 2 per cent. and 8 per cent. of the population.

Since the war efforts have been made both at governmental and voluntary levels to improve the situation. Hundreds of additional beds have been made available. The Singapore Anti-Tuberculosis Association (S.A.T.A.) opened a modern chest clinic in 1952 as a centre for diagnosis and extensive out-patient treatment, while the Government "Rotary" Clinic at the Tan Tock Seng Hospital has a large turn-over.

In 1954 Australia was asked to assist the Government of Singapore in making a preliminary survey of the tuberculosis problem in the Colony.

The purpose of the survey, directed by Sir Harry Wunderly, the Commonwealth Director of Tuberculosis, was to indicate to the Ministry for Health the seriousness of the tuberculosis problem in Singapore. It was decided that a "sample" case finding programme would be conducted, by X-raying 50,000 adults over the age of 14 of varying population character. Four areas were selected to indicate broadly the incidence of tuberculosis in Singapore. In addition, it was agreed that all active cases found should be placed under treatment. Finally, it was hoped that an adequate scheme of tuberculosis control for the whole island could be set in operation at a later date.

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Preliminary arrangements included the appointment of a whole-time tuberculosis director (C.E.S.), the setting up of a case register, and the sending to Australia of radiographers and laboratory technicians to gain experience in Mass X-ray work.

Australia undertook, under Colombo Plan aid, to send a team comprising a chest physician of consultant status (C.H.), a chest physician experienced in mass miniature radiography (C.R.), two senior radiographers, and a bacteriologist.

Publicity

One month before the survey began, an intensive propaganda campaign was initiated under the direction of one of us (C.E.S.), and a complete system of home visiting was carried out by Health Visitors assisted by voluntary workers. They distributed leaflets (in four languages), gave pep talks, and handed out appointment cards. It was stressed that the survey was free, voluntary and confidential.

Local authorities had expressed the fear that local superstitions, dread of disease and of loss of employment would be potent bars to general participation. On the other hand, there is a tuberculosis allowance scheme in Singapore, which ensures to sufferers with a good prognosis a reasonable livelihood while they are undergoing treatment. Surprisingly, the response exceeded all expectations. The ready co-operation of the people at all stages was, indeed, one of the outstanding features of the campaign.

This true community survey commenced on July 1, 1958, and finished on October 24, 1958. Though it was estimated some 350 would attend daily, in point of fact there were often over 500, and at times well over 100 X-rays were taken in an hour. The staffs rose to the occasion and the work proceeded smoothly. There were practically no breakdowns of equipment and only 595 persons had X-rays considered technically unsatisfactory, mostly due to shutter failures. They were recalled, but 137 failed to re-attend. The miniature films were of very high standard.

Procedure and Staff

Persons not living in the areas also turned up for an X-ray. To safeguard the epidemiological study of the Survey, cards of the " non-residents " were marked accordingly and analysed separately. Each person attending for an X-ray had to produce an identity card. If pregnancy was obvious this was entered on the card and also information of previous tuberculosis history.

The miniature films with abnormalities were cut out and forwarded to the Control Unit at Tan Tock Seng Hospital.

All films showing heart abnormalities, and some with non-tuberculous conditions, were forwarded to the General Hospital to be called up for further investigation.

Persons found with lesions deemed to be healed or of doubtful significance were grouped under the heading of " scars " and were advised by letter to have a further X-ray in three to twelve months.

Singapore medical personnel allotted to assist were numerous, but only one, Dr. C. E. Smith, worked full time with the Survey, of which he was in charge, and responsible to the Minister for Health.

A third reading was undertaken by the three of us, who acted as adjudicators between the first two readers. It was felt that this ensured a fairly high standard of accuracy in X-ray reading.

Findings

A total of 54,812 persons, of whom 50,673 were residents and 4,139 non-residents, was X-rayed by the two 70 mm. (Odelca-Watson) Units, using spools of forty frames and a photo-timer, in sixty-four working days. The closure of the Units ten days or more before the advertised date, as the target was reached, obviously prevented many more from being X-rayed. It would not be unreasonable to suggest that well over 90 per cent. of the available population would have accepted the Survey.

Table 1 shows the estimated population from the 1957 Census, the numbers X-rayed, and the number of working days in the four areas.

Table 1

Area	*Eligible population*	*No. X-rayed residents*	*No. X-rayed non-residents*	*Total X-rayed*	*No. of working days*
1. Jalan Sultan ..	24,985	20,288 = 81·5%	1,246	21,534	23
2. China Town ..	24,240	20,758 = 85·6%	450	21,208	27
3. Bukit Panjang ..	7,011	5,128 = 73·1%	1,023	6,151	14
4. Geyland Serai ..	5,387	4,499 = 83·5%	1,420	5,919	
Total ..	61,623	50,673 = 82·2%	4,139	54,812	64

The general results of the surveys are presented in Table 2. It will be noted that for purposes of statistical accuracy care has been taken to group separately previously known cases of tuberculosis.

Table 2

Diagnosis		*Residents*			*Non-residents*			*Grand total*	
		Males	*Females*	*Total*	*Males*	*Females*	*Total*		
Pulmonary tuberculosis	Active new	1,209	369	1,578	133	24	157	1,735	2,057
	Active known ..	250	53	303	16	3	19	322	
	Inactive new ..	947	457	1,404	107	33	140	1,544	2,064
	Inactive known ..	293	84	377	30	2	32	520	
	"Scars"	1,088	617	1,705	105	38	143	1,848	
Under investigation		31	12	43	3	1	4	47	
Non-tuberculous conditions ..		351	298	649	68	33	101	750	
Heart abnormalities		585	662	1,247	48	37	85	1,332	
Refused to attend for investigation		361	219	581	47	11	58	639	

An overall total of 2,057 active cases of tuberculosis was diagnosed, of which 1,735 were new cases and 322 previously known. The highest prevalence of active cases was found amongst residents in Chinatown (4·8%) and the lowest in Geylang Serai (1·1%) populated by Malays. The percentage of active tuberculosis amongst non-residents X-rayed in the survey was higher (4·2%) than amongst residents (3·7%): see Table 3.

Table 3 shows the numbers X-rayed and the numbers and percentages considered to be active in the four areas. The figures in brackets in this and following tables represent previously known cases.

TABLE 3

Area	*No. X-rayed residents*	*Number active*	*%*	*No. X-rayed non-residents*	*Number active*	*%*
1. Jalan Sultan ..	20,288	744 (127)	3·6	1,246	78 (11)	6·7
2. China Town ..	20,758	994 (162)	4·8	450	22 (1)	4·9
3. Bukit Panjang ..	5,128	95 (12)	1·8	1,023	35 (4)	3·4
4. Geylang Serai ..	4,499	48 (2)	1·1	1,420	40 (3)	2·8
Total	50,673	1,881 (303)	3·7	4,139	175 (19)	4·2

The final results of investigation of the non-tuberculous conditions are not yet available, except for the heart abnormalities.

A total of 667 patients with suspected abnormal heart shadows was examined at the Cardiac Clinic of the General Hospital. Briefly, 323 were found to have some form of cardiac disorder, the chief groups being 68 with rheumatic, 65 with hypertensive and 59 with congenital heart disease.

Analysis of Active Cases (Residents)

A total of 29,400 males was examined and 1,459 active cases were detected (4·9%) and 21,273 females with 422 active cases (1·9%). It is of interest to note that over 1,000 more Malaysian females than males were X-rayed in Geylang Serai, whilst only 267 Indian and Pakistani females were X-rayed in all four areas as compared with 2,974 males. Table 4 shows the total

TABLE 4.—RESIDENTS

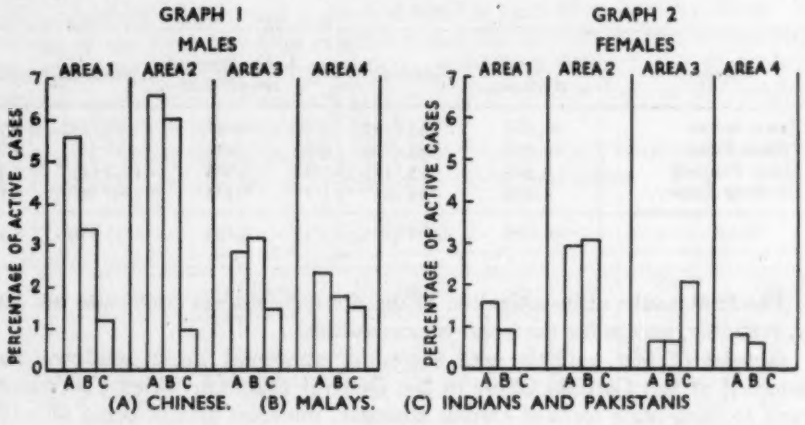
Race	*Male*			*Female*			*Total*		
	No. X-rayed	*No. active*	*%*	*No. X-rayed*	*No. active*	*%*	*No. X-rayed*	*No. active*	*%*
Chinese	23,774	1,347 (236)	5·6	17,419	395 (51)	2·2	41,193	1,742 (287)	4·2
Malaysians ..	2,563	73 (6)	2·8	3,549	25 (2)	0·7	6,112	98 (8)	1·6
Indians and Pakistanis ..	2,974	39 (8)	1·3	267	2	0·7	3,241	41 (8)	1·2
Others	89	Nil	—	38	Nil	—	127	Nil	—
Total	29,400	1,459 (250)	4·9	21,273	422 (53)	1·9	50,673	1,881 (303)	3·7

number of males and females X-rayed in the four areas according to race and the number and percentage of active tuberculosis detected (Graphs 1, 2 and 3.)

The racial distribution of residents X-rayed was as follows:

Chinese	41,193 (81·3%)
Malaysians	6,112 (12·1%)
Indians	3,241 (6·4%)
Others	127 (0·2%)

The highest incidence of tuberculosis was amongst Chinese males (5·6%), followed by Malaysians (2·8%), and Indians and Pakistanis (1·3%).



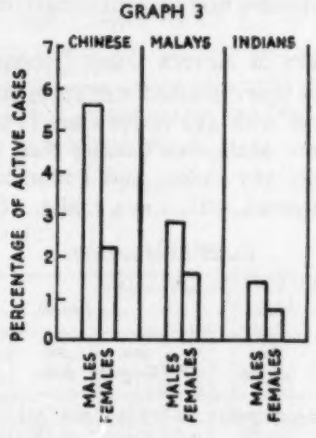


Table 5 is an analysis of cases found in each area, according to race and sex.

It can be seen from Table 6 and Graph No. 4 that the highest incidence of active tuberculosis, 10·7 per cent., occurred in males in age groups 50 years

and over as against 3·6 per cent. under the age of 50. In females the difference was not so marked, being 2·8 per cent. and 1·7 per cent.

Analysis of Active Cases (Non-residents)

The incidence amongst all males was 5·5 per cent. and females 1·7 per cent. The prevalence of active tuberculosis in males over 50 years old was 14·7 per cent. and in females it was only 1·7 per cent. in the same age group.

Table 5

	Males			*Females*			*Total*		
	No. X-rayed	*No. active*	%	*No. X-rayed*	*No. active*	%	*No. X-rayed*	*No. active*	%
Area 1 *Jalan Sultan*									
1. Chinese ..	9,870	542 (96)	5·5	6,974	142 (23)	2·2	16,844	684 (119)	4
2. Malaysians	1,028	35 (5)	3·4	957	10 (1)	1·4	1,985	45 (16)	2·3
3. Indians and Pakistanis	1,351	15 (2)	1·1	47	Nil	—	1,398	15 (2)	1·1
4. Others ..	42	Nil	—	19	Nil	—	61	Nil	—
Total area 1 ..	12,291	592 (103)	4·8	7,997	152 (24)	1·9	20,288	744 (127)	3·6
Area 2 *China Town*									
1. Chinese ..	11,215	730 (132)	6·5	8,504	242 (27)	2·8	19,719	972 (159)	4·9
2. Malaysians	117	7	6	69	2	2·9	186	9	4·8
3. Indians and Pakistanis	820	13 (3)	1·6	31	Nil	—	851	13 (3)	1·1
4. Others ..	2	Nil	—	Nil	Nil	—	2	Nil	—
Total area 2 ..	12,154	750 (135)	6·2	8,604	244 (27)	2·8	20,758	994 (162)	4·8
Area 3 *Bukit Panjang*									
1. Chinese ..	2,310	66 (8)	2·9	1,569	8 (1)	0·5	3,879	74 (9)	1·9
2. Malaysians	298	10	3	224	1	0·5	522	11	2
3. Indians and Pakistanis	601	8 (3)	1·3	99	2	2	700	10 (3)	1·4
4. Others ..	24	Nil	—	3	Nil	—	27	Nil	—
Total area 3 ..	3,233	84 (11)	2·5	1,895	11 (1)	0·6	5,128	95 (12)	1·8
Area 4 *Geylang Serai*									
1. Chinese ..	379	9	2·4	372	3	0·8	751	12	1·6
2. Malaysians	1,120	21 (1)	1·9	2,299	12 (1)	0·5	3,419	33 (2)	0·9
3. Indians and Pakistanis	202	3	1·5	90	Nil	—	292	3	1
4. Others ..	21	Nil	—	16	Nil	—	37	Nil	—
Total area 4 ..	1,722	33 (1)	1·9	2,777	15 (1)	0·5	4,499	48 (2)	1·1
Grand total ..	29,400	1,459 (250)	4·9	21,273	422 (53)	1·9	50,673	1,881 (303)	3·7

TABLE 6.—GRAND TOTAL (RESIDENTS)

Age group	Total males			Total females		
	No. X-rayed	*No. active cases*	%	*No. X-rayed*	*No. active cases*	%
14	799	3	0·3	551	3 (1)	0·5
15–19	5,564	76 (3)	1·3	3,258	22 (2)	0·6
20–24	4,413	110 (10)	2·4	2,921	35 (1)	1·1
25–29	3,770	148 (20)	4·1	2,555	36 (3)	1·4
30–34	3,134	136 (22)	4·3	2,170	47 (7)	2·1
35–39	2,566	142 (23)	5·4	1,941	51 (5)	2·6
40–44	2,289	188 (41)	8·2	1,823	54 (6)	2·9
45–49	2,404	190 (34)	7·9	1,936	58 (12)	2·9
Total under 50 yrs.	24,939	993 (153)	3·6	17,155	306 (37)	1·7
50–54	1,744	187 (42)	10·7	1,583	49 (5)	3·0
55–59	1,319	134 (29)	10·1	1,154	37 (6)	3·2
60–64	682	84 (19)	12·3	643	16 (1)	2·4
65 and over ..	567	59 (7)	10·4	622	12 (4)	1·9
Total over 50 yrs.	4,312	464 (97)	10·7	4,002	114 (16)	2·8
Not stated ..	149	2	1·3	116	2	1·7
Grand total	29,400	1,459 (250)	4·9	21,273	422 (53)	1·9

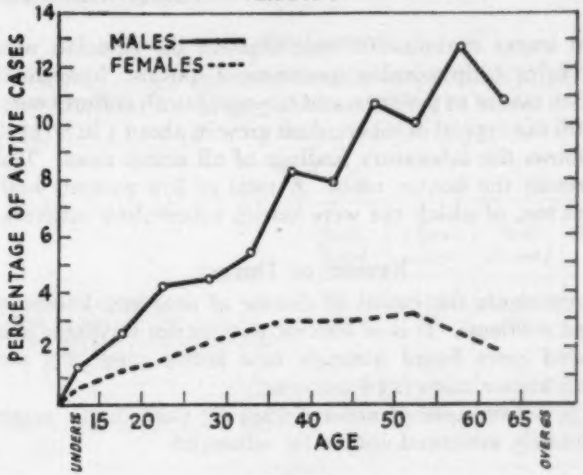
LABORATORY FINDINGS

Patients recalled for medical interview were asked to produce a specimen of sputum for immediate microscopic examination. If the patient was unable to produce sputum or the specimen on inspection was unsatisfactory, a laryngeal swab was done according to the method described by Nassau. A modified Lowenstein-Jensen medium was used for cultures.

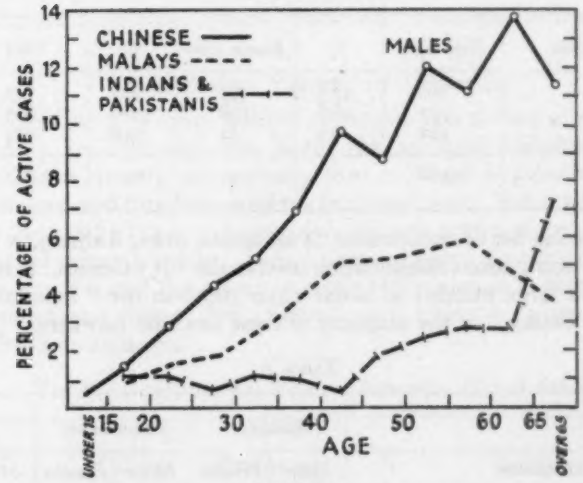
TABLE 7.—LABORATORY FINDINGS OF ACTIVE CASES

	Residents	*Non-residents*	*Total*
1. Direct microscopy +ve	356 (74)	54 (6)	410 (80)
2. Sputum culture +ve	260 (33)	35 (1)	295 (34)
3. Laryngeal swab +ve	96 (7)	7	103 (7)
4. Gastric contents +ve	4	—	4
	716 (114)	96 (7)	812 (121)
5. Direct microscopy −ve	104 (18)	11 (3)	115 (21)
6. Sputum culture −ve	546 (86)	40 (3)	586 (89)
7. Laryngeal swab −ve	358 (29)	27 (6)	385 (35)
8. No tests done	82 (48)	—	82 (48)
9. Unknown	75 (8)	1	76 (8)
Grand total	1,881 (303)	175 (19)	2,056 (322)

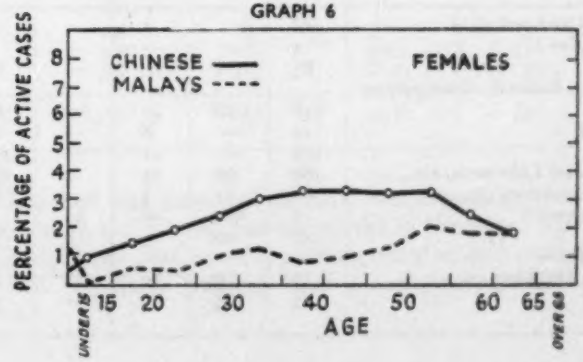
GRAPH 4



GRAPH 5



GRAPH 6



If the first smear examination was negative the clinician would request the patient to bring early morning specimens of sputum. Sputum cultures had a contamination rate of 10 per cent. and laryngeal swab cultures only 1 per cent. Acid-fast bacilli not typical of tuberculosis grew in about 1 in 80 of the cultures.

Table 7 shows the laboratory findings of all active cases. The figures in brackets represent the known cases. A total of 812 patients had a positive bacteriological test, of which 121 were known tuberculosis sufferers.

Extent of Disease

Table 8 represents the extent of disease of new and known active cases found amongst residents. It is of interest to note the relatively small number of far advanced cases found amongst new active cases (8·5 per cent.) as compared with known cases (23·8 per cent.).

Of the 175 active cases of non-residents 67 were in the minimal stages, 81 were moderately advanced and 27 far advanced.

Table 8.—Residents

Extent of disease	*New cases*	%	*Known cases*	%	*Total*	%
Minimal	719	45·5	73	24·1	792	42·1
Moderate	727	46·6	158	52·1	885	47·1
Far advanced ..	132	8·5	72	23·8	204	10·8
Total	1,578	100	303	100	1,881	100

The following list of occupations of all active cases, Table 9, is taken from the Malayan occupations classification used in the 1957 Census. It is disturbing to find such a large number of active cases (604) in the "Sales and Related Occupations Group," as the majority of these are food hawkers.

Table 9

	Residents		*Non-residents*		*Totals*	
Occupation	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*
1. Professional and technical	18	—	2	—	20	—
2. Administrative	5	—	—	—	5	—
3. Clerical	85	2	11	—	96	2
4. Sales and Related Occupations Group	546	18	40	—	586	18
5. Agricultural	21	—	8	—	29	—
6. Transport	122	—	11	—	133	—
7. Craftsmen and Labourers, etc. ..	469	66	53	2	522	68
8. Service, Recreation, etc.	62	11	5	1	67	12
9. Home Housework	2	307	—	21	2	328
10. Students	47	10	5	2	52	12
11. Economically— Inactive, Disabled, etc.	71	2	12	1	83	3
12. Not Stated	25	5	2	—	27	5

Treatment

Up to March 31, 1959, 234 patients were hospitalised; 1,555 were receiving treatment as Out-Patients and 53 patients failed to attend for treatment, as per Table 10.

Table 10

	Jalan Sultan	*China-Town*	*Bukit Paniang*	*Geylang Serai*	*Total*
Number of cases hospitalised	161	53	9	11	234
Number of cases treated as Out-patients ..	532	907	81	35	1,555
Number of cases failed to attend for treatment	16	34	3	—	53
Total	709	994	93	46	1,842
Additional diagnosed active cases since March 31, 1959	35	—	2	2	39
Grand total	774	994	95	48	1,881

Tuberculin Testing of Children

It was possible to arrange a mass tuberculin skin testing of children under the age of 14, immediately after X-ray surveys were completed in Areas 1 and 2 but not in Areas 3 and 4 owing to an outbreak of poliomyelitis.

Six-hundred and fifty-five children (59·8 per cent.) had a positive reaction and were X-rayed (Table 11); 36 cases showed active primary tuberculosis and 60 healed primary lesions. It had been arranged for the positive reactors under the age of 3 and the others showing active disease to receive treatment. Four hundred and twenty-five children with negative tuberculin reactions received BCG vaccination.

Table 11.—Tuberculin Tests of Children (Jalan Sultan)

Age groups in years	*Tuberculin tested (Heaf)*	*Positive*	%	*Negative*	%
0–2 ..	192	60	31·2	132	68·8
3–6 ..	398	182	45·7	216	54·3
7–14 ..	506	413	81·6	93	18·4
Total ..	1,096	655	59·8	441	40·2

Seven hundred and sixty-nine children had tuberculin tests in Chinatown immediately after the Survey was completed in the area. Five hundred and four children (66 per cent.) had a positive reaction and were X-rayed. Two hundred and fifty-three children with a negative reaction received BCG vaccination.

Discussion

From the aspect of case-finding, the survey may be considered a successful one. A total of 2,058 persons was detected with pulmonary tuberculosis deemed to be active. The overall percentage, 3·75, though high, was less than expected, but we think it can be taken as a fair sample of the incidence of tuberculosis in Singapore, and this was our chief target.

It is to be noted that 639 persons recalled did not attend for examination, of whom 172 were suspected of having active tuberculosis. Our figures therefore are conservative in some respects, *e.g.* bacteriology.

However most persons attended the clinics, and were placed under treatment where necessary. It was disappointing to us that only a relatively small percentage, some 13 per cent., were admitted to hospital, but the reasons for this are multiple: (1) the patients were reluctant; (2) the medical staff have become " conditioned " to domiciliary therapy; (3) there were staff difficulties. None the less, the isolation of the infectious case must be regarded as a major goal in tuberculosis eradication in Asia as elsewhere, especially in densely overcrowded populations.

Apart from those requiring treatment, a large number of apparently inactive cases has been collected. These will require regular supervision, but any breakdown should be found and treated quickly.

Attention is drawn to the high rate in Chinese males (5·6 per cent.) rising in the older age groups to startling figures, *e.g.* 50-54 age 12 per cent.; 60-64, 13·7 per cent. Presumably these indicate a breakdown of earlier disease from the wear and tear of increasing years, as is now being found in Caucasian males. The Malaysians, Indians and Pakistanis show the same tendency, but the rates are only half those of the Chinese.

It is noteworthy that in high density areas, as shown on the graphs, not only was incidence higher, but an equal proportion of Chinese and Malay males was affected.

It was surprising to find that clinicians estimated the number of active and inactive cases to be practically equal. In most surveys the inactive far outnumber the active cases. It might be reasoned that under the local conditions healing is less complete and that more cases smoulder. Only a long-term follow-up could decide the significance of these figures.

As with most Mass Surveys, the proportion of " minimal " cases is relatively high, at 42 per cent., but " advanced " cases were fewer than expected, 10·8 per cent. The prompt institution of treatment could be expected to be successful in most cases.

Bacteriological standards were high, and it is considered that the yield of 35 per cent. of bacteriologically proven cases was a good one, especially as the great majority of patients attended the laboratory only once, either having an " on-the-spot " specimen of sputum taken, or alternatively, a laryngeal swab and culture. The results from the latter justified the use of this technique in preference to gastric lavage cultures, being more simple, time-saving, and acceptable to the patients.

A matter of concern was the high number of active cases found among

shop employees and food hawkers. The danger of spreading infection from this group is obvious. Workshops are very overcrowded. In one spool of 40, among 8 active cases found, 7 came from one printer's shop.

Some 62 per cent. of 1865 contact children in two areas under 14 were found to have a positive Heaf test, but it is not possible to state that this figure is significantly higher than for random groups of children in Singapore. Noteworthy is the fact that none of these children appeared ill, though 36 were deemed to have active primary lesions. These, together with all reactors under the age of 3, were given Isoniazid chemo-prophylaxis. Arrangements have been made to follow-up these children and a later report should be interesting.

The number of persons found to have other respiratory diseases, and in particular cardiac disease, illustrates again the value of a multiphasic survey in the field of clinical medicine.

Summary

A pilot survey to estimate the incidence of tuberculosis was conducted in Singapore from July to October 1958.

Four " sample " areas, estimated to yield some 50,000 persons over the age of 14, were selected for community survey.

A total of 54,812 persons was X-rayed in 64 working days. Of these 50,673 were residents of the districts surveyed, being 82·2% of the possible total. There were in addition 4,139 non-residents.

Among the residents, 1,881 cases of active pulmonary tuberculosis were detected, and 175 among non-residents, an overall total of 2,058, or 3·75% of the population surveyed.

The racial distribution among residents was: Chinese 81·3%, Malaysians 12·1%, Indians and Pakistanis 6·4%.

The incidence in males was nearly 2½ times that in females: 4·9% to 1·9%. The incidence in Chinese males was 5·6%, Malaysians 2·8% and Indians and Pakistanis 1·3%.

The incidence of active disease was considerably greater in the crowded urban areas (4·8% and 3·6%) than in the suburban and rural areas (1·8% and 1·1%).

Only 10·8% of all active cases were in the far advanced stage, and 42·1% were considered minimal.

Bacteriological proof was obtained in 35% of the cases.

By March 31, 1959, 1,789 patients were being given treatment. Of these 234 had been admitted to hospital and 1,555 were being treated as out-patients.

Among employed people, the largest groups with active tuberculosis were in " Sales and related occupations " 604 cases, craftsmen and labourers 590, home duties 330.

Inactive cases found numbered 2,064, against 2,057 active cases.

Of 667 films suspected to show an abnormal cardiac shadow 323 cases of heart disease were found.

1,865 children under 14, contacts of cases found, were Heaf tested and 1,159 gave a positive reaction.

Acknowledgments are due to the Department of External Affairs of the Australian Commonwealth Government, the staff of the Australian Commission in Singapore and members of the Ministry for Health of the Singapore Government for assistance given us; to Sir Harry Wunderly, formerly Director of Tuberculosis in Australia, whose wise and practical ground plan enabled the Survey to proceed; to the other members of the Colombo Plan team, who worked strenuously and enjoyed most friendly relations with local personnel; to the Physicians and Radiologists of the Singapore General and Tan Tock Seng Hospitals, and of S.A.T.A.; to the Government Statistician's Department; to various other bodies, voluntary organisations and individuals too numerous to mention. The enthusiastic co-operation of all who assisted in the Survey, often beyond the bounds of duty, was as praiseworthy as it was stimulating. Our relations with workers at all levels were entirely happy, and the experience for us was a rewarding one.

Brit. J. Dis. Chest (1960) **54**, 247.

THE INITIATION OF CHEMOTHERAPY IN PULMONARY TUBERCULOSIS IN WEST AFRICANS

HOSPITAL AND AMBULANT TREATMENT COMPARED USING STREPTOMYCYCLIDINE-ISONICOTINIC ACID HYDRAZIDE

By W. J. Bell

From the Tuberculosis Research Unit, West African Council for Medical Research, Accra, Ghana

The general aspects of the problem of pulmonary tuberculosis in West Africa have been outlined recently: Owen *et al.* (1958) have enumerated a number of factors that qualify successful ambulatory treatment in Nigeria; Bell (1959) has discussed the problem of management in Ghana with particular reference to the pattern of disease in the Ghanaian and to the therapeutic facilities available; an assessment of the incidence of active disease has been made by the World Health Organisation (1957 and 1958) and Hetreed (1959). Essentially, the problem is related to a high urban and rural incidence of advanced disease in a population that is scattered, migratory and largely illiterate outside the larger towns, and to a shortage of hospital beds and of facilities for pulmonary surgery.

Ambulatory treatment of the majority, using combinations of drugs in the definitive sense, is now established practice. It has been suggested by O'Beirn (1959) that such hospital beds as are available should be reserved for the initial short-term treatment of the more acutely ill, as is a general practice in many parts of West Africa.

While there can be no argument about the desirability of admitting to hospital those who are seriously ill, there is controversy with regard to those who are in relatively good condition and who are not required to occupy a bed for surgical, social or other reasons.

Plan of Investigation

Indigenous West African males, between the ages of 15 and 40, with pulmonary tuberculosis involving more than one lung zone and believed to be of recent origin and previously untreated, and excreting tubercle bacilli fully sensitive to streptomycin and isoniazid, were eligible for investigation. Any with intercurrent disease of such gravity as to be likely in itself to qualify prognosis were not accepted.

Patients who fulfilled the criteria for acceptance were allocated, at random, to an in-patient or out-patient treatment group. Those chosen for in-patient treatment were admitted strictly on a basis of rotation according to the number of beds available. Those for whom beds were not available were removed from the in-patient list and were not included in the investigation.

(*Received for publication February* 8, 1960.)

Of 100 cases chosen, 33 were finally allocated in-patient treatment, and 56 out-patient treatment.

Treatment Groups

In-patient Group.—All in this group were kept in hospital for a period of twelve weeks from the commencement of treatment and given daily injections of streptomycyclidine-isonicotinic acid hydrazide (Streptohydrazid). Patients were allowed up for toilet purposes and to sit up for one hour daily. Otherwise, strict bed rest was enforced. Standard African hospital dietary was supplied and patients were not permitted to supplement this with food from outside.

Out-patient Group.—Patients in this group were required to report daily, for a period of twelve weeks, for injections of Streptohydrazid. No restriction was placed on their activity, and if any felt well enough to continue work, he was free to do so. Each was encouraged to take his normal diet, and no supplementary feeding was given.

In both groups, any incidental disease (malaria, helminthic infestation, schistosomiasis, etc.) was treated, and standardisation of such treatment was attempted. After the three months' period of treatment, chemotherapy was continued in all cases on an out-patient basis.

Since the variables under investigation were hospital and ambulatory treatment, it was necessary to ensure that each patient received uninterrupted and identical anti-tuberculous drug therapy.

Investigations

The following investigations were undertaken before the commencement of drug treatment: general clinical investigation; investigation of the sputum bacteriology (direct examination of sputum concentrates, culture and sensitivity tests); chest radiograph; examination of stool, urine and peripheral blood; Kahn and rapid sickling tests. Apart from Kahn and sickling tests, these were repeated monthly.

All investigations were undertaken by the staff of the Tuberculosis Research Unit at the Kumasi Central Hospital, Ghana. Bacteriological investigations were undertaken by one technician, and all other laboratory investigations by another. In the interest of radiographic comparability, and in the absence of cooled processing tanks, all radiographs were exposed by one technician and developed singly by sight.

Comparability of Treatment Groups

The state of the two groups at the commencement of treatment is summarised in Table I. In almost all respects they are highly comparable. Overall, the in-patients were rather iller than the out-patients in respect of general clinical condition and body weight. In respect of the grouped figures of radiological involvement, there is no practical difference.

TABLE I.—COMPARABILITY OF IN-PATIENT AND OUT-PATIENT GROUPS AT START OF TREATMENT

	In-patients No.	%	*Out-patients* No.	%
Numbers in groups	33		56	
General clinical condition:				
severely ill ..	3	9·1	6	10·7
poor	16	48·5	17	30·4
fair and good ..	14	42·4	33	58·9
	(χ^2 3·04: $P>0·2$)			
Bacteriology of sputum:				
direct positive ..	33	100·0	56	100·0
culture positive ..	32	97·0	53	94·6
bacterial resistance	0		0	
Mean body weight (lb.)	116·788		111·536	
standard deviation	14·36		20·35	
	($t=1·423$: $P>0·05$)			

	In-patients No.	%	*Out-patients* No.	%
Numbers in groups	33		56	
Radiology:				
*Lung zones involved:				
2 zones	2	6·1	9	16·1
3 „	5	15·2	10	17·9
4 „	13	39·3	14	25·0
5 „	3	9·1	7	12·5
6 „	10	30·3	16	28·5
	(χ^2 3·57: $P>0·3$)			
†Cavity classification:				
Category I	0	0	0	0
„ IIA	1	3·0	3	5·4
„ IIB	3	9·1	3	5·4
„ IIC	3	9·1	13	23·1
„ IIIA	2	6·1	2	3·6
„ IIIB	8	24·2	14	25·0
„ IIIC	16	48·5	21	37·5
	($\chi^2=4·48$ $P>0·3$)			

* Joint Tuberculosis Council.
† Protocols for the Chemotherapy of Tuberculosis.

RESULTS

Changes in the General Condition

All assessments of general condition were made by two physicians separately, and the results were compared. There was no way of avoiding bias in clinical assessment in this investigation, as the in-patients were assessed in hospital wards, the out-patient group at out-patient clinics. Nevertheless, the comparability of assessment was high. Changes in the general condition are summarised in Table II.

TABLE II.—CLINICAL STATE MONTHLY FROM START OF TREATMENT

Months from start of treatment	*Numbers in groups* *I.P.	*O.P.	*Clinical state* *Severely ill* I.P.	O.P.	*Poor* I.P.	O.P.	*Fair to good* I.P.	O.P.
			%	%	%	%	%	%
0	33	56	9·1	10·7	48·5	30·4	42·4	58·9
1	33	56	0	0	3·0	7·1	97·0	92·9
2	33	56	0	0	6·1	1·9	93·9	98·1
3	33	56	0	0	3·0	1·9	97·0	98·1

* I.P. = In-patients. O.P. = Out-patients.

After one month of treatment, almost all in each group were in good condition and remained so throughout the period of treatment. Those still classed as in poor condition after three months' therapy were all patients who at the time of admission to the investigation were severely ill, malnourished, and had gross disease radiologically. At the end of three months' treatment there were no practical differences between the two groups.

Changes in Body Weight

The mean weight of the patients monthly from the start of treatment is given in Fig. I.

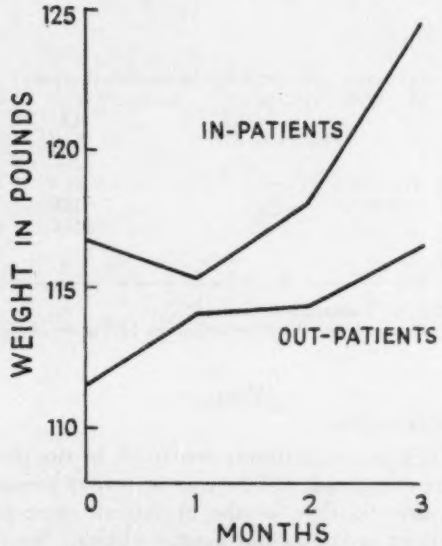


FIG. 1.—Changes in weight monthly from start of treatment.

After an initial slight fall, the mean in-patient weight rose steadily, and more rapidly. After three months' treatment they had gained 7·8 lb. overall, against an out-patient gain of 5·2 lb. None of the differences in any month is statistically significant.

Bacteriological Results

The results of monthly bacteriological examinations of sputum are summarised in Table III.

Direct examination: There was a steady fall in the bacterial content of the sputum over the period of treatment and there was no significant difference in positivity at the end of three months. One patient reverted to positive at the third month, and he was shown to be resistant to streptomycin and isoniazid. None of the differences in any month is statistically significant.

Cultural examination: There was a steady fall in positivity in each group, and at the end of the period of treatment there was no material difference. Sputum was concentrated by the NaOH method and two slopes were inoculated in each case. Only locally prepared fresh solid medium was used, and no culture was labelled negative until the completion of twelve weeks' incubation.

TABLE III.—DIRECT AND CULTURAL EXAMINATION OF SPUTUM MONTHLY FROM START OF TREATMENT

Months from start of treatment	*Numbers in groups*		*Direct examination of concentrates*		*Cultural examination*	
			Positive		*Positive*	
	**I.P.*	**O.P.*	*I.P.*	*O.P.*	*I.P.*	*O.P.*
			%	%	%	%
0	33	56	100	100	97·0	94·6
1	33	56	60·6	57·1	51·5	59·9
2	33	56	21·2	25·0	25·0	18·2
3	33	56	18·2	14·3	17·9	16·1

* I.P. = In-patients. O.P. = Out-patients.

Bacterial resistance: Sensitivity estimations were undertaken monthly on all positive cultures obtained. Three patients developed resistance to both streptomycin and isoniazid: one out-patient was partially resistant after one month of treatment, and fully so after three months; one out-patient and one in-patient developed partial resistance at the second month, and both were still partially resistant at the third month.

Radiological Changes

Table IV summarises radiological changes monthly from the start of treatment in terms of improvement (slight, moderate or considerable), no change or deterioration. Monthly radiographs were compared with pre-treatment films and read, according to pre-arranged criteria of improvement or otherwise, by two physicians responsible for the clinical management of the cases. To avoid bias in reading, pairs of films applying to this investigation were mixed with similarly marked pairs from patients undergoing treatment with other combinations of drugs, and read without knowledge of the regimen applying.

In each category a larger proportion of the out-patients than of the in-patients had improved to a moderate and considerable extent at the three months point, but the differences are not significant. Overall, 81·8 per cent. of in-patients showed improvement against 87·5 per cent. of out-patients. Almost one-fifth of the in-patients had not changed after three months, and one out-patient showed deterioration with increase in exudative shadowing and in the size of cavities at the second month, persisting to the third month.

TABLE IV.—RADIOLOGICAL CHANGE MONTHLY FROM START OF TREATMENT

Months from start of treatment	Numbers in groups		Improvement						No change		Deterioration	
			Considerable		Moderate		Slight					
	*I.P.	*O.P.	I.P.	O.P.	I.P.	O.P.	I.P.	O.P.	I.P.	O.P.	I.P.	O.P.
			%	%	%	%	%	%	%	%	%	%
1	33	56	0	0	12·1	8·9	63·6	67·8	24·3	23·3	0	0
2	33	56	0	3·5	21·2	23·2	60·6	55·4	18·2	16·1	0	1·8
3	33	56	3·0	10·7	21·2	28·6	57·6	48·2	18·2	10·7	0	1·8

* I.P. = In-patients. O.P. = Out-patients.

Resistance to streptomycin and isoniazid was demonstrated in this case after one month of treatment.

After three months, 24·2 per cent. of cavities in the in-patient group had closed or blocked (12·1% closed; 12·1% blocked) against 19·6 per cent. in the out-patient group (12·5% closed; 7·1% blocked). Of those neither closed nor blocked, 66·7 per cent. of in-patients' and 72·3 per cent. of out-patients' cavities had shrunk. One case in each group showed marked thinning of cavities. Two in-patients and three out-patients showed no cavity change.

None of the differences in respect of general radiological or cavitary changes is significant.

Discussion

This investigation was planned to obtain some definition of the usefulness of initial hospitalisation in the chemotherapy of pulmonary tuberculosis in West Africans, by comparing the relative rates of clinical and radiological change, and of sputum conversion, in similar groups treated in hospital or as out-patients, and given identical chemotherapy.

A regimen of daily streptomycin and isoniazid was chosen. As there was doubt that out-patients might not take all oral isoniazid prescribed, an injectable combination of streptomycin and isoniazid was given in the form of Streptohydrazid. This preparation was developed from an interaction between streptomycin and isoniazid (Pennington *et al.*, 1953) and offers the activity of 1 gramme of streptomycin and 236 milligrammes of isoniazid in a single injection. In concentrated solution, the preparation largely maintains its chemical combination, but rapid and complete hydrolysis appears to occur at body temperature. The therapeutic efficacy of the preparation was demonstrated by Payne *et al.* (1956), and Shubin and Heiken (1956).

Shortage of hospital beds in West Africa and a high tuberculous morbidity preclude hospital admission for many, and it is not always possible to clear beds even for those who are acutely ill. That there is some sanction for applying out-patient chemotherapy to severely ill patients is evidenced by the fact that no out-patient failed to report for daily injection over the three months' period of treatment, and that there was no significant overall difference in the rate of improvement in the two groups according to the criteria chosen.

With regard to general clinical change, almost all in each group were in fair to good condition after one month of therapy. The small number who remained in poor condition were severely ill patients with gross radiological involvement at the commencement of treatment. No accurate assessment of differences in in-patient and out-patient feeding was possible, but the dietary standard of the former was better in respect of regularity of feeding, caloric value, and in the levels of protein, carbohydrate and vitamins. Fat intake appeared equal in the two groups. The superiority of the in-patient diet may account for the slight progressive increase in the weight of in-patients from the second month onwards. The caloric requirement of the out-patients was much higher, however, as all had to come to hospital daily, and as many continued work. The initial fall in the in-patient weights may be related to a number of indefinable factors. The West African takes some weeks to settle in hospital, for he does not always understand and often fears the strange disciplined environment, he is unhappy at separation from his family and his friends, and his normally haphazard feeding habits are altered. It has recently been suggested by Barlovatz (1959) that plenty of food and vitamins do not materially improve the results of antibiotic treatment in Africans in the Belgian Congo, and this is largely substantiated by this controlled short-term investigation. Haddock (1959) had a contrary experience in Tanganyika where he found that those who did not do well on controlled out-patient chemotherapy invariably did better on admission to hospital, although he does not outline his criteria of betterment.

The rates of sputum conversion, on the evidence of direct examination of concentrates and culture, were the same. The three cases who developed bacterial resistance had gross radiological disease with multiple large cavities. The one case exhibiting radiological deterioration had a progressive *in vitro* resistance to both streptomycin and isoniazid from the end of the first month.

There was little difference in the rate of radiological change in the two groups. More out-patients improved to a considerable extent, and less showed no change after three months' treatment. The groups were small, and individual variation is reflected in the figures. The differences can be accounted for by the slightly greater weight of individuals with gross disease and multiple cavitation in the in-patient group at the commencement of treatment. The rates of cavity closure were much the same in the two groups and, in relation to original cavity size, the figures for closure are higher than those given by Livings (1959) for patients treated with streptomycin and isoniazid. Tomography was undertaken in all cases at the end of three months' treatment.

According to the criteria chosen, hospitalisation was not shown to alter progress materially during the first three months of treatment. Nevertheless, the analysis does not mirror the considerable discomfort and difficulty experienced by the more seriously ill patients in travelling to hospital daily for injections. Further work is being undertaken to define the effect of initial hospital treatment on the long-term definitive chemotherapy of pulmonary tuberculosis in Africans.

Summary

A controlled study has been undertaken to determine the usefulness of initial short-term hospitalisation in the chemotherapy of pulmonary tuberculosis in West African males.

Thirty-three patients were treated in hospital for a period of twelve weeks, and fifty-six entirely on an out-patient basis for the same period. Patients were allocated to in-patient and out-patient treatment groups irrespective of clinical condition. Identical daily combined chemotherapy was given to each group.

No significant differences in the rates of clinical improvement, of weight gain, of radiological change nor of sputum conversion were demonstrated.

My thanks are due to Dr. J. H. Mendes of the Ghana Government Medical Service for help with the clinical management of the cases, and to Messrs. Chas. Pfizer Ltd., for supplying all the Streptohydrazid used in the investigation.

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SURGICAL TREATMENT FOR PULMONARY TUBERCULOSIS IN CHILDHOOD

By H. C. Nohl and S. J. Steel

From the London Chest Hospital and High Wood Hospital for Children, Brentwood

During the past decade considerable advances have been made in the surgical treatment of tuberculosis. Before the introduction of anti-tuberculous chemotherapy, surgery was rarely considered in children and was confined to cases of chronic pulmonary tuberculosis. Surgical procedures were practically limited to collapse therapy, including the division of adhesions by thoracoscopy in artificial pneumothorax, extrapleural pneumothorax and rarely thoracoplasty. The advent of chemotherapy has not only radically changed the medical treatment of tuberculosis in children, as in adults, but has made the resection of diseased lung tissue a feasible surgical procedure. This has raised new problems in relation to the role of surgery in the treatment of tuberculosis in children. While there is general agreement about its place in the active stages of chronic pulmonary tuberculosis, the indications for resection of damaged lung tissue after prolonged chemotherapy are still under discussion. As yet there has been no unanimity in the views expressed on the treatment of primary tuberculosis. The lack of correlation of the radiological appearances with the underlying lung pathology in the past has been partly responsible for differences in opinion.

Since Thomas (1952) published his classic paper on surgical treatment of primary pulmonary tuberculosis, many others have discussed the various aspects presented by both the primary and chronic forms of this disease in childhood. Some of these, however, based their conclusions on small numbers of surgically treated cases. It is the purpose of this paper to present the results of a relatively large series of surgically treated children from High Wood Hospital, including both primary lesions and chronic pulmonary tuberculosis, in the hope of throwing new light upon some of the problems involved and clarifying the indications for surgical intervention.

Material

During the ten years from 1949 to 1958 inclusive, 3,107 children under the age of 16, mostly suffering from the various pulmonary forms of tuberculosis, have been treated by Dr. F. J. Bentley and Dr. W. F. Richards at High Wood Hospital. Seventy-one had surgical treatment under the care of Mr. Holmes Sellors at the London Chest Hospital and these patients have been selected for detailed study.

Of these 71, 18 were suffering from primary tuberculosis or its complications and 53 had the adult-type lesions of chronic pulmonary tuberculosis. The age, sex and extent of the disease of these patients are shown in Table I.

The duration of hospital treatment and chemotherapy before and after

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TABLE I.—AGE, SEX AND EXTENT OF DISEASE

Pulmonary tuberculosis	*Total patients*	*Average age on admission*	*Sex distribution*		*Radiological classification of pulmonary tuberculosis on admission*				
					*High Wood Classification**				
			Male	*Female*	*Enlarged hilar glands*	*Primary complex*	*Segmental lesions*	*Post-tuberculous syndrome*	*Empyema*
Primary ..	18	5 years	5	13	3 (with obstructive emphysema)	2	8 3 (with obstructive emphysema)	4	1

					Ministry of Health Classification (December 1956)†					
					A.1	*A.2*	*A.3*	*B.1*	*B.2*	*B.3*
Chronic	53	12 years	25	28	14	3	1	13	9	13

* Bentley, Grzybowski and Benjamin (1954), "Tuberculosis in Childhood and Adolescence."
† Ministry of Health Classification (December 1956):

A=Bacteriologically negative.
B=Bacteriologically positive.

1=Total area of disease not exceeding $\frac{1}{3}$ of one lung in aggregate.
2=Total area of disease not exceeding $\frac{2}{3}$ of one lung in aggregate.
3=Total area of disease exceeding $\frac{2}{3}$ of one lung in aggregate.

operation are shown in Table II. All the patients received treatment with chemotherapy, with the exception of two who had extra-pleural pneumothoraces in 1950-51. Those in the earlier years were treated with relatively short courses of streptomycin and PAS. The majority, however, had the benefit of treatment with streptomycin, PAS and isoniazid, using two of the

TABLE II.—DURATION OF HOSPITAL TREATMENT AND CHEMOTHERAPY

Pulmonary tuberculosis	*Total patients*	*Average stay in hospital*	*Average duration of chemotherapy*			*Total*
			Before operation	*After operation*	*Ambulant*	
Primary	18	13 months	22 weeks	22 weeks	0	44 weeks
Chronic	53	19 months	39 weeks	14 weeks	44 weeks*	97 weeks

* Twenty-two patients with chronic pulmonary tuberculosis (40%) had a course of chemotherapy with PAS and isoniazid after leaving hospital.

drugs at a time in various combinations, usually changing at each three-monthly period, except where drug-resistant organisms or hypersensitivity were encountered. The average duration of chemotherapy was 44 weeks in the patients with primary lesions and 97 weeks in those with chronic pulmonary tuberculosis.

INDICATIONS FOR SURGICAL TREATMENT

Only a few children were treated surgically in the earlier years of the period under review and most of these had extrapleural pneumothoraces performed. A more accurate estimate of the proportion of children receiving surgical treatment is therefore obtained by analysis of the figures during the second half of the decade when anti-tuberculous chemotherapy had widened the choice of treatment.

During the five years from 1954 to 1958 inclusive, a total of 515 children suffering from various forms of primary tuberculosis or its complications, excluding miliary tuberculosis and simple pleural effusions, were treated at High Wood Hospital and 17 of these received surgical treatment (3·3 per cent.). Another 309 children were treated for chronic pulmonary tuberculosis and 45 of these received surgical treatment (14·6 per cent.).

Primary Tuberculosis

This form of tuberculosis has long been recognised as relatively benign (Adler and Richards, 1953; Bentley *et al.*, 1954; Macpherson and Lutwyche, 1950). The radiological shadows in the lung fields are usually transient and the hilar adenitis resolves satisfactorily over a period of months. Yet complications due to dissemination, although rare, are of serious consequence. "Collapse/consolidation" of lobes or segments is not infrequent and, although these segmental lesions may resolve completely, bronchography shows that the incidence of residual bronchial abnormalities is high. Hughes and Ray (1958)

examined 99 consecutive cases, of which 65 had bronchograms, and in 34 of these bronchial abnormalities were found. Hill and Pearson (1959) did bronchograms on all children who had evidence of pulmonary collapse two to four years previously and found abnormal bronchi in 47 out of the 71 cases (55·2 per cent.). They stress that the majority of children remained asymptomatic.

Opinion differs regarding the incidence of local extension of the primary infection. Some authors record relatively low figures such as the 17 per cent. reported by Bentley *et al.* (1954). On the other hand Hughes and Ray (1958) found that 35 per cent. of their cases developed complications. They were specially impressed by the danger of enlarged glands, as complications occurred in 64 per cent. of patients with simple hilar adenitis.

It is, therefore, not surprising that conflicting views are held on the place of surgery in primary tuberculosis. There are those who advocate thoracotomy in cases with enlarged hilar glands for prophylactic reasons (Giraud *et al.*, 1956; Thomas, 1952), or in those with persistent collapse (Thomas, 1952; Huish, 1956; Cleland, 1956; Chesterman, 1957), while others favour a more conservative attitude (Bentley *et al.*, 1954; Cameron *et al.*, 1957; Jeune, 1956; Hill and Pearson, 1959).

The indications for surgical treatment in the present series are set out in Table III. No child was operated on for prophylactic reasons merely because of enlarged hilar glands and all those selected for surgery presented symptoms due to the various complications of primary tuberculosis. Thus a third of the patients had obstructive emphysema with persistent or recurrent symptoms of wheezing and/or cyanosis, which, as concluded by Dip Singh and Richards (1957), were considered absolute indications for thoracotomy. These symptoms were so severe in two children, both under the age of 2, that they caused considerable anxiety and one was prepared for an emergency thoracotomy. In both these children bronchoscopy had shown endobronchial granulations blocking one of the main bronchi and attempted removal of this obstruction via the bronchoscope was unsuccessful. Failure to relieve the obstruction bronchoscopically in a high proportion of similar cases has been the experience of Seal and Thomas (1956) and Bentley *et al.* (1954). Nine other children had persistent collapse and bronchiectasis causing symptoms in spite of adequate and prolonged chemotherapy (see Table II). The indications for surgery in the remaining cases were one tuberculous empyema and two large cavitating primary foci.

The majority of these cases still had bacteriological or histological evidence of active tuberculosis at the time they came to operation. Thus a third of the children had either positive sputum just before operation or a positive culture was obtained from the resected specimen. The remainder, except for five, had histological evidence of active tuberculous lesions as shown by tuberculous granulation tissue or caseation. Seal and Thomas (1956) found that the radiological shadows in segmental lesions were more often due to tuberculous parenchymal involvement than to simple collapse in the cases which they resected and this accords with our experience.

TABLE III.—INDICATIONS FOR SURGICAL TREATMENT

Pulmonary tuberculosis	*Total patients*	*Large cavitated primary focus*	*Obstructive emphysema causing persistent symptoms*		*Persistent collapse and bronchiectasis*		*Empyema*
			with enlarged hilar glands	*with segmental lesions*	*Segmental lesions*	*Post-tuberculous syndrome*	
Primary	18	2	3	3	5	4	1

Pulmonary tuberculosis	*Total patients*	*Cavitated tuberculoma*	*Persistent cavitation after an average of more than 6 months' chemotherapy*	*Large residual lesions after an average of 6 months' chemotherapy*	*Persistent collapse and tuberculous bronchiectasis*	*Empyema*
Chronic	53	5	21 3 satisfactory but unsuccessful artificial pneumothoraces 3 unsatisfactory artificial pneumothoraces 5 failed inductions of artificial pneumothoraces 1 persistent positive sputum after chemotherapy 2 positive sputum at operation but no chemotherapy	10 4 failed inductions of artificial pneumothorax 4 hypersensitive to anti-tuberculous drugs 1 persistent positive sputum after chemotherapy	16 1 resistant organisms 1 hypersensitive to anti-tuberculous drugs 3 persistent positive sputum 1 diabetes mellitus	1

Chronic Pulmonary Tuberculosis

Here the indications for surgery were very similar to those which govern the selection for this form of treatment in adults. These are summarised in Table III. In some of the patients the persistence of large residual lesions or unclosed cavities, despite adequate chemotherapy, played a large part in the ultimate decision for surgical interference. In many of the earlier cases induction of an artificial pneumothorax had either failed or the established pneumothorax did not achieve satisfactory control of the disease. Other reasons for resection were intolerance to the anti-tuberculous drugs or drug resistant organisms. Finally, irreversible lung damage in the form of atelectasis and bronchiectasis or completely destroyed lungs causing symptoms were considered definite indications for surgery. Histological evidence of active tuberculosis was demonstrable in 38 of the 40 cases and in the one tuberculous empyema.

Surgical Procedures

Extra-pleural Pneumothorax

This form of collapse therapy was employed in the early cases of this series, when resection was not fully established. The complication rate was high (see Table V). The ultimate result, although it achieved control of the disease in most instances, was not nearly as satisfactory as in the resection cases.

Adenectomy

When there is bronchial obstruction due to pressure or ulceration and discharge of caseous material from adjacent involved lymph nodes into the bronchus, bronchoscopy is frequently unsuccessful in relieving the obstruction, an observation made also by Seal and Thomas (1956). This is not surprising in view of the large volume of caseous material in the lymph nodes as compared with the small perforation into a child's narrow bronchus.

Surgery in these cases where bronchoscopy has failed has proved to be more successful, but is sometimes technically difficult. The lymph nodes are often adherent to the pulmonary vessels, so that it has often been found safer to incise the lymph node capsule and evacuate its contents, rather than to excise the gland *in toto*. This method has already been recommended by other authors (Thomas, 1952; Cleland, 1956). On removal or evacuation of these glands a hole is often left in the related bronchus, due to the already existent perforation. It is then necessary to close this defect by suture, covering the suture-line with surrounding tissue such as gland capsule and pleura. Sometimes there is at first glance no apparent glandular enlargement to account for the bronchial obstruction until the mediastinum is explored, when either the subcarinal or para-œsophageal nodes are found to have perforated the medial aspect of the main bronchus. Adenectomy may either be carried out alone or in conjunction with resection of diseased lung parenchyma.

TABLE IV.—SURGICAL PROCEDURES

Pulmonary tuberculosis	Total patients	Pneumonectomy or lobectomy					Segmental or wedge resection		Decortication		Adenectomy		Thoraco-plasty	Extra-pleural pneumo-thorax
		Pneumonectomy	2 Lobes	1 Lobe	Lobectomy and segmentectomy	Lobectomy and adenectomy	Segmentectomy or wedge resection only	Segmentectomy or wedge resection and adenectomy	Decortication only	Decortication and segmental resection	Adenectomy only	Adenectomy and sleeve resection of bronchus		
Primary	18	2	1	3	2	1	3	3	1	1	2	2	1	11
Chronic	53		1	10	1		26							

When there is actual stenosis of the bronchus present with healthy lung tissue beyond the constriction, a sleeve resection of the bronchus may give good results (Jackson, Jones and Sellors, 1955).

Lung Resection

The resection of residual tuberculous areas or bronchiectatic segments or lobes can present similar difficulties on account of matted glands at the hilum. For these reasons the dissection was on occasions deliberately carried out away from the hilum, so that the vessels could be secured further out in the lung tissue. At other times it has been found advantageous to start the dissection from the periphery towards the hilum by cutting and ligaturing the lung tissue seriatim and thus not proceeding strictly in the true segmental plane. This has made the resection of diseased lung tissue much safer and has proved completely satisfactory. The raw surfaces of the lung were often approximated by fine mersilene sutures so that little if any air leak resulted.

The surgical procedures which were carried out are tabulated in Table IV. One thoracoplasty was done. This operation is usually considered as contra-indicated in the growing child, because of the consequent scoliosis (Sellors, 1944). In this instance it was a six rib thoracoplasty done on a boy of 14 and did not result in any deformity but achieved arrest of the disease. There were two children who had to have a decortication for tuberculous empyemata. One followed a primary effusion, the other occurred as part of chronic pulmonary tuberculosis. Huish (1956) could find no record in the literature of decortication being used to deal with the results of primary effusion and was unsuccessful in the two cases in which he tried it.

TABLE V.—POST-OPERATIVE COMPLICATIONS

Pulmonary tuberculosis	*Total patients*	*Surgical procedures*	*Post-operative complications*									
			Atelectasis	*Hemorrhage*	*Intra-pulmonary hematoma*	*Pneumothorax*	*Hydro-pneumothorax*	*Apical air space*	*Persistent effusion*	*Tuberculous empyema*	*Skin wound rupture*	*Paralytic ileus*
Primary	18	All procedures (see Table IV)	—	—	—	—	—	—	—	—	—	—
Chronic	53	12 Lobectomies	1	1	—	1	—	—	—	—	—	—
		26 Segmental resections	—	—	4	—	—	3	—	—	1	1
		11 Extra-pleural pneumothoraces	—	2	—	—	1	—	1	1	—	—
		4 Other procedures	—	—	—	—	—	—	—	—	—	—

Complications and Results

Complications

Apart from extra-pleural pneumothoraces post-operative complications were few (see Table V). Intra-pulmonary hæmatomata resulting from suture of raw lung surfaces and the occasional apical air space were always transient and therefore of no significance. Atelectasis of a remaining lobe was rare.

The smoothness of the post-operative convalescence as compared with similar surgery in the adult was impressive. In all but a few patients the final radiological results were good.

Follow-up

The results are set out in Table VI.

Table VI.—Follow-up after Surgical Treatment

Pulmonary tuberculosis	*Total patients*	*Death*	*Relapse*	*Remained well*	*Observation years after surgery*								
					0–1	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9
Primary	18	0	1	17	6	5	3	2	0	0	1	0	1
Chronic	53	0	2	51	6	7	11	8	6	5	3	5	2

Primary Tuberculosis

There were no deaths and all the children did well, except one girl who had only four weeks, pre-operative chemotherapy and developed renal and cervical glandular tuberculosis three years after the operation. This patient had further treatment with anti-tuberculous drugs and is now well and working.

Chronic Pulmonary Tuberculosis

In this group there was also no death. There were only two relapses and both of these followed extra-pleural pneumothoraces. One who received no pre-operative chemotherapy developed a tuberculous empyema after the operation and later spread occurred in both upper lobes while her sputum was still positive. With subsequent chemotherapy her disease was arrested. In the other patient, who had only fifteen weeks' pre-operative streptomycin and PAS, the extra-pleural pneumothorax was complicated by a hydro-pneumothorax. Refills were discontinued two and a half years later, but within nine months of termination of the pneumothorax she had a positive laryngeal swab culture. She also was given chemotherapy and her disease is now considered quiescent.

Summary

Seventy-one children who were treated for pulmonary tuberculosis at High Wood Hospital between 1949 and 1958 and who had surgical treatment at the London Chest Hospital were selected for study. Eighteen of these were

suffering from primary tuberculosis or its complications and 53 had chronic pulmonary tuberculosis. All except two received chemotherapy.

The indications for surgery are discussed. Between 1954 and 1958, 3·3 per cent. of children with primary tuberculosis or its complications and 14·6 per cent. of those with chronic pulmonary tuberculosis were selected for surgical treatment.

The various surgical procedures employed in treating primary and chronic pulmonary tuberculosis and the results are discussed. In patients selected for surgery resection is considered to be the method of choice, together with adenectomy in the case of enlarged glands causing symptoms. Extra-pleural pneumothorax has been abandoned and thoracoplasty is contra-indicated in children.

The relative freedom from post-operative complications and the good radiological results obtained by comparison with similar surgical treatment in adults is emphasised.

All the patients were followed up. There were no deaths. Only one child with primary tuberculosis failed to do well and developed renal and cervical glandular tuberculosis three years after operation. Among the children with chronic pulmonary tuberculosis treated surgically only two relapsed, both following extra-pleural pneumothoraces.

The importance of adequate chemotherapy is stressed.

It is concluded that surgical treatment should be confined to a small number of patients with persistent symptoms due to the various complications of primary tuberculosis, while in children with chronic pulmonary tuberculosis the indications for surgery are the same as those in adults.

We wish to thank Dr. F. J. Bentley, Dr. W. F. Richards and Mr. T. Holmes Sellors for their kind permission to publish the details of their patients and for their very helpful criticism.

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250 CASES OF RESECTION FOR PULMONARY TUBERCULOSIS

By H. J. Beard

From the Department of Thoracic Surgery, Kelling Hospital, Holt, Norfolk

This paper is a report on the first 250 cases of resection for pulmonary tuberculosis performed in Kelling Hospital between March 1950 and August 1957, the minimum follow-up period being two years.

Indications for the resection of a lesion and for the particular operation to be performed are various and must to a considerable extent depend on the personal views of the physicians and surgeons concerned.

The indications for pneumonectomy are the best defined, destroyed lung being the chief. In our experience the main difficulty has been in assessing the ability of the remaining lung to support life without making the patient a respiratory cripple, and trying to avoid a recrudescence of any disease which may have been present in that lung.

For lobectomy or segmental resection the indications are wider and subject to a more personal interpretation. The round focus, approximately 2 cm. or more, is usually removed, preferably by segmental or wedge resection. In the 250 cases under review the writer distinguishes two groups of cases: those with tuberculosis of fairly recent onset and those with old-standing disease, often of ten or more years' duration. The latter group, the smaller of the two, contains several patients in their fifties and the chief indications for operation have been repeated hæmoptyses or a positive sputum from time to time. The positive sputum was a special indication in those patients with a young family around them and in those with a health responsibility to the community. They were mostly upper lobe lesions showing fibrosis and contraction. Bronchiectasis in the contracted lobes was the usual cause of the hæmorrhage and positive sputum, although some patients had a lung cavity which had been present for several years. In a very few patients a change in the quality of the radiographic shadow led us to operate, malignant changes having been considered and differential diagnosis not being possible. Malignancy was found in one case.

These patients with old-standing disease have been the most exacting to operate upon. Many were in relatively good health and not seriously incommoded by their disease, yet the positive sputum endangered their livelihood. Technically the operation can be difficult on account of fibrosis and old calcified glands. In these conditions there is risk of a vascular accident which may turn a planned lobectomy or segmental resection into pneumonectomy. This happened once in the series. There were some two dozen of this old-standing disease group, mostly in their forties and fifties, of whom one

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died from pulmonary embolus, another had a cerebral incident and two later showed relapse of disease. The remainder did well.

The second group in the indications for lobectomy or segmental resection are those patients with tuberculous disease of more recent onset. For convenience this group is further subdivided into those cases who have been in sanatorium before, mostly younger patients. During their first period of treatment it has been agreed that the lesion should be given a chance to heal by conservative means, and most of them do so. Those breaking down or failing to remain sputum negative have been readmitted and after a short period of medical treatment had a resection operation. Without exception these patients have done well. The second group consists of patients in sanatorium for the first time. Several factors influence a decision to operate. The chief indication is in the patient with localised disease who, after four to six months' treatment, has an unclosed cavity or irregular solid areas of

TABLE I

	Cases	*Operation deaths*	*Late deaths*	*Relapses*
Pneumonectomy ..	60	9	4	4
Lobectomy	86	5	2	11
Segmental	104	2	1	1

Of the late deaths four were due to causes other than tuberculosis.

disease which serial radiographs show to be unchanged. Often there has been disease in both lungs and we have planned to operate on each side, but often, once the worse side has been done, the other has improved without interference. In fact in this series only four patients have had two resection operations.

Apart from purely pathological indications there have been instances where operation was advised because of the patient's work, such as handling foodstuffs or teaching. A few have been done because the work was heavy and of a nomadic nature. On occasion a clear indication has been the chest physician's opinion that the patient would not take his drugs or come in to sanatorium a second time if needed.

Early in the series some patients had an existing artificial pneumothorax, the reason for operation being that the lesion was not responding as it should or that a thickened pleura was forming. Sometimes a pneumothorax was induced with the idea that if at thoracoscopy it was not considered satisfactory, then resection was to be performed.

A small number of patients were diabetics and this was an added reason for operating.

In all cases the administration of anti-tuberculous drugs both before and after operation has, as elsewhere, gone through various phases. In the early days some patients had as little as one month of streptomycin and PAS.

Most patients were sputum negative at the time of operation; this will be referred to later.

There were 143 male and 107 female cases. Table I shows the figures for the three types of operation, and in Table II the annual figures show the operative trends. Pneumonectomies and lobectomies increased up to 1953, after which pneumonectomies decreased rapidly. From 1953 there was an increase in segmental resections. Looking at the figures there is a marked contrast between the four years prior to 1953 and the four years following. After 1953 the figures are more even, with segmental resections topping the numbers. It was thought that most operation deaths would be found in the first four-year period, but in fact there are eight deaths in each period.

The different types of operation are next discussed.

TABLE II

	1950	*1951*	*1952*	*1953*	*1954*	*1955*	*1956*	*To Aug. 1957*
Pneumonectomy ..	7/2 D	10/2 D	14/1 D	17	2	6/3 D	4/1 D	0
Lobectomy	3/2 D	1	15	23	15/2 D	11	11/1 D	7
Segmental	0	2	4	9/1 D	30/1 D	24	21	14
Totals	10	13	33	49	47	41	36	21

D=Deaths.

The Pneumonectomies. The chief reason for the preponderance of this operation in the early years was the overhang of many advanced cases, the majority of whom were females, from the pre-streptomycin era. As well as destroyed lung a few patients had secondarily infected tuberculous empyema and one early pneumonectomy was for stenosis of the left main bronchus which would today be treated by sleeve resection. It must be emphasised that in many of these patients the pneumonectomy represented a truly last ditch operation. They were grave risks, some died but more survived to do well.

There were nine operation deaths in sixty pneumonectomies, a death rate of 15 per cent. The average age of the patients who died was 26, the oldest being 32. Causes of death were: four due to broncho-pleural fistula and empyema, two to cardio-respiratory failure, one died during operation, one from pulmonary embolus and one from œsophageal fistula. Of the four late deaths, two were due to pulmonary tuberculosis five years after operation, one was due to right heart failure four years after operation, and the remaining death was from suicide five years later.

The complications of the operation were four empyemas, in addition to the four deaths from this cause, and two of these still have a tube *in situ*. These cases were all done in the first four-year period.

Twenty-six patients had a thoracoplasty, this being done concomitantly in 14 cases and a few weeks later in the others.

Forty-seven pneumonectomy patients are living and of these six have noticeable shortness of breath, but no patient has serious respiratory embarrassment. Most of the patients are working, including wives doing housework,

and some of these have had children. The ages of the patients at the time of operation ranged from 5 to 60.

The Lobectomies. There were eighty-six lobectomies and the five deaths, average age 35, give just under 6 per cent. death rate. The two late deaths were non-tuberculous, carcinoma cervix and nephritis.

They comprised sixty upper and twenty-six lower lobectomies, with twice as many right upper as left upper lobectomies. This is because the anterior and lingula segments can usually remain on the left side, whereas on the right it is sometimes unsatisfactory to leave the anterior segment alone, even though it is healthy.

There were three deaths among the upper lobectomies, one due to fistula and empyema. In this patient there was a lung cavity present and the sputum was positive prior to operation. Another death was due to heart failure in a case with advanced tuberculosis; the third death, due to pulmonary embolus, was mentioned under the old-standing tubercle group.

Serious post-operative complications were few, but one patient still has an empyema sinus.

TABLE III.—LOWER LOBECTOMIES

	R.L.L.	*Cav. present.*	*L.L.L.*	*Cav. present.*
Nos.	13	4	13	7
Fistula or empyema complication ..	1	1	4	3
Relapse	0	0	3	1
Deaths	0	0	2	1

A space reducing thoracoplasty was performed in twelve of the upper lobectomies. Occasionally the thoracoplasty was done as a planned procedure three or four weeks before the lobectomy.

Two patients were pregnant at the time of their lobectomy and did well.

The figures for lower lobectomies were so disquieting that they have been given a separate table (Table III) and this, together with sputum information gives, I believe, reason why so many went wrong. Of the twenty-six lower lobectomies fourteen had either a positive sputum or a cavity present or both at the time of operation. In four out of five empyema and fistula cases following lower lobectomy there was both a cavity and positive sputum. All were young patients and in each the physician looking after the case was concerned that, despite prolonged medical treatment, they were not improving.

The two lower lobectomy deaths were due to fistula and empyema.

The Segmental Resections. Of these there were 104 with two deaths, a rate of 1·9 per cent. One death was due to pulmonary embolus in a 36-year-old male. The other death, a male aged 22, was never satisfactorily explained, but is counted as due to operation, for after it he was never really well and died six months later in another hospital, the cause of death being given as tuberculosis. The one late death was due to carcinoma of the bladder.

The outstanding feature of the segmental resections is the absence of relapses. Even the one relapse shown followed a wedge resection and was a re-opening of a cavity in the opposite lung.

Many of the segments resected came from lobes which were extensively diseased. When stripping out such segments, cavities and caseous masses have from time to time been inadvertently torn open, yet the operation has remained singularly free of any tuberculous complication. Two cases developed localised non-tuberculous empyema which resolved with aspiration. Early in the series chests were on two occasions reopened because it was thought lung re-expansion was too slow; this would not be done today. One case had to be reopened for hæmorrhage. One female age 54, mentioned under the old-standing disease group, was hypertensive and had a cerebral incident during operation. Though well she is left with some slowness of speech.

At about two-thirds of the operations two or more segments were removed, but the residual space following such resections has proved less of a problem than was expected. Either as a planned part of the operative procedure or because of residual space a small thoracoplasty has been performed on 10 patients. Bickford and others (1957) said that thoracoplasty should always be performed if two or more segments were resected. Our experience does not seem to indicate that. Up to 1955, for both lobectomy and segmental resection, the operation was often preceded by a pneumoperitoneum and then either at operation or a few days later a phrenic crush was performed.

Discussion

The relapses. Of these 250 resection cases 16 patients later had a relapse of their disease. Half of these were sputum positive at the time of operation. In the pneumonectomies five of the six relapses, including the two late tuberculous deaths, had radiographic evidence of disease in the other lung when operated upon and only one case had a thoracoplasty. None of the eight upper lobectomies which relapsed had had a thoracoplasty. Some of these cases had palpable disease in the remaining lobes, but this applies equally well to many which did not relapse.

The average time from operation to the time of relapse was two years three months. It is noticeable that all except three of these late spreads occurred in patients operated on in the first four-year period.

The most important factor in these relapses is that all the patients except one had three months' or less post-operative anti-tuberculous drug therapy. Since prolonged post-operative drug treatment was instituted only one case has relapsed. There is no doubt that in the early years the patients did not have enough drug treatment either before or after operation. The part played by drug resistance in the relapses is largely unknown, for in the first few years routine sensitivity tests were not done. The organisms of one lower lobectomy case which relapsed were known to be resistant wholly or partly to all three

drugs. A few resistant cases, including one pneumonectomy, have remained well.

Complications and Mortality. Of the complications, fistula and empyema were the most serious. There were 15 in the series, mostly connected with right side pneumonectomies, and 7 died. All except three of these complications occurred in the first four years when chemotherapy was inadequate. In the report on Major Surgery for Pulmonary Tuberculosis by Francis and Curwen (1958) it was shown that infected fistulæ were more common in cavitated and sputum positive cases. Earlier, Gordon (1954) had stressed the importance of pre-operative chemotherapy in the prevention of fistula formation. More recently Levendel and others (1959) report a 5·4 per cent. empyema fistula rate in 926 operations. They believe fistulæ to be a local manifestation of tuberculosis and found the fistula rate higher in patients whose disease was not showing radiological improvement prior to operation. The comments made above on the lower lobectomies (Table III) lead to similar conclusions.

The overall operation mortality rate for the 250 cases was 6·4 per cent. Three deaths were due to pulmonary embolus, a high preponderance, and all occurred within one year. It is interesting to note in comparison that not once in over 2,000 thoracoplasty operations has the writer seen a death from pulmonary embolus. Wynne-Edwards (1959) in a wide experience of resection and thoracoplasty has only seen one death from pulmonary embolus following thoracoplasty. Francis and Curwen (1958) show a higher pulmonary embolus rate following resection than collapse measures, and most of the latter were thoracoplasties consisting of two or more operations.

Conclusions

One of the pleasant surprises in this review has been the finding of how well most of the grave risk pneumonectomies have done. Another has been that the segmental resections did well despite the fact that the drug treatment of the early cases was, by today's standards, very inadequate. The lobectomy figures are, however, disappointing in the matter of relapses. The number of these might have been reduced if more thoracoplasties had been done after the upper lobectomies. The post-lobectomy thoracoplasty performed, where the first rib is left intact and short segments of the next two or three ribs are resected, interferes very little with the function of the remaining lobe or lobes.

Since August 1957, where this review ends, the number of resection operations for pulmonary tuberculosis has decreased, but a further 76 resections have been performed without a death or serious complication following lobectomy and segmental procedures. Although decreasing in numbers we still find resection has a place in the treatment of pulmonary tuberculosis. It tends now to be reserved for those patients where, after chemotherapy, cavities or nodular areas of disease remain, but age, social and economic background of the patient seem increasingly to influence the decision. Surprisingly there is, too, the occasional pneumonectomy still being performed on patients whose disease originated in the pre-streptomycin era.

Summary

Two hundred and fifty cases of resection for pulmonary tuberculosis are reviewed. Indications for resecting a lesion are presented and the figures for pneumonectomy, lobectomy and segmental resection are analysed. The overall operative mortality was 6·4 per cent. Sixteen patients had a relapse of their disease at an average time of just over two years from operation. Bronchial fistula and empyema was the most serious operative complication and this problem is discussed. These complications and relapses have been greatly reduced in numbers since the introduction of more adequate chemotherapy. The present position of resection for pulmonary tuberculosis is mentioned.

I am greatly indebted for their help to my colleagues Mr. E. C. Wynne-Edwards, who shared with me the operations on these patients, and to our anæsthetist Dr. A. I. Ward. I should also like to express my gratitude to all the physicians concerned for their help in following up these patients.

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SKIN AND BUCCAL PIGMENTATION, PULMONARY TUBERCULOSIS AND STEATORRHŒA

By A. W. Lees

From Ruchill Hospital, Glasgow

Increased pigmentation of the skin may occur in a variety of conditions, but the co-existence of buccal pigmentation is virtually pathognomonic of Addison's disease (Simpson, 1956). The following case proved an exception to this rule, despite the presence of such confirmatory phenomena as asthenia, low blood pressure, impaired ability to handle a water load, and the development of overt pulmonary tuberculosis. It appears unusual enough to be worthy of record.

Case Record

A male, aged 50 years, was admitted to Ruchill Hospital on complaining of a productive cough and recent lassitude and loss of weight.

In 1937 a diagnosis of acute nephritis had been made in another hospital and the records showed that at that time he was œdematous and had albumen and casts in the urine. His B.P., however, was only 130/70 and it was noted that he had a tanned complexion. In 1950 he was again admitted to the same hospital with a complaint of lassitude, regurgitation of food, and heartburn. His B.P. was 80/58, his skin was markedly pigmented, and he had well-marked pigmentation of the buccal mucosa. No urinary abnormality was found. Radiological examination showed no evidence of pulmonary tuberculosis or of suprarenal calcification. Although biochemical tests were not conclusive, Addison's disease was diagnosed on the basis of the clinical findings. Treatment with DOCA and added dietary salt produced marked symptomatic benefit, and later DOCA implants were given. At a follow-up examination in 1950, a chest film showed infiltration in the right upper lobe, and tubercle bacilli were found in the sputum. The patient subsequently received anti-tuberculous therapy at various institutions, but he could not be induced to take drugs regularly. Because of lack of co-operation he had no treatment for Addison's disease after 1950.

When admitted to hospital on 13.10.58 the patient was thin and feeble. There was an obvious, generalised dusky pigmentation of the skin, accentuated in creases and on exposed areas. There were well-marked patches of pigmentation on the buccal mucosa. Signs of consolidation were present over the right upper lobe. The B.P. was 95/65, but the cardiovascular system was otherwise essentially normal. The patient stated that although for a few days he had been having only one or two bowel movements a day, for a fortnight before that he had had diarrhœa with four or five loose motions a day. He also stated that for some weeks he had had cramp in his legs and that in the past few days his hands had occasionally become stiff and had taken up a peculiar position. Chvostek's and Trousseau's signs were positive and the serum Ca. was 7·3

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mg./100 ml. After admission the patient had several episodes of spontaneous tetany (accompanied by laryngeal stridor on one occasion) which were relieved by intravenous Ca. gluconate. He had at first two loose stools per day; in a week or so, one per day. A chest film showed fibrotic disease and a cavity in the right upper lobe; tubercle bacilli, resistant to streptomycin, isoniazid and PAS, were recovered from sputum on several occasions, but never from stools.

The following were among the investigations carried out. The total fat excreted as stearic acid in 24 hours when the patient was on an ordinary mixed diet was 65 g. on 26.10.58; 49 g. on 27.10.58; 40 g. on 28.10.58; 20 g. on 26.11.58; 19.3 g. on 27.11.58; 16·3 g. on 28.11.58; and 20·7 g. on 5.4.59 (normal <6 g. according to Cooke and French, 1958). On 11.11.58 the total fæcal fat was 42·2 g. in 24 hours and of this 31·6 g. (74%) was split, and 10·6 g. (26%) unsplit; abundant fat globules, but no undigested muscle fibres were seen on microscopic examination. Johnston's film test for duodenal trypsin was positive up to 1 : 180 dilution (low normal). Serum amylase was 100 Gomori units (normal). A barium meal follow-through showed no evidence of a fistula, blind loop or regional ileitis; the small bowel mucosal pattern was compatible with idiopathic steatorrhœa.

Examination of serum electrolytes showed low levels of calcium and potassium: the lowest figure for calcium was 6·2 mg./100 ml. (25.11.58), and the lowest figure for potassium 2·8 m.equiv./l. (5.12.58); the values for other electrolytes were always within, or not much outside, the normal range. There was no clinical evidence of vitamin deficiency, but saturation with vitamin C was hard to achieve: significant amounts of daily doses of 600 mg. of vitamin C by mouth did not appear in the urine until the eleventh day and only irregularly thereafter, whereas in scorbutic subjects on the same dosage saturation is reached in 6 to 7 days (Lowry, 1952). A blood sugar curve following the ingestion of 50 g. of glucose showed no tendency to flatness: the fasting blood level was 108 mg./100 ml., 1½ hours after the ingestion of the glucose, it was 156 mg./100 ml., and 2½ hours afterwards it was 102 mg./100 ml. Prothrombin time was normal (18 secs., control 16 secs.). X-ray films of the skeleton showed generalised osteoporosis most marked in the peripheral bones, and examination of an iliac crest biopsy specimen (B.E.C. Nordin), confirmed the marked demineralisation. The serum acid phosphatase was normal (2·8 KA units %).

Blood examination on 7.11.58 showed: R.B.C. 4 M.; Hb., 13·3 g. %; W.B.C., 7,900; P.C.V., 41 mm.; M.C.H.C., 32%; Poly., 51%; Lymph., 42%; Myel., 1%; Mono., 1%; Eos., 5%. The red blood cells looked normal. Bone marrow smears showed no abnormality: erythropoiesis was normoblastic and leukopoiesis was normal; a moderate number of plasma cells was present. Sections showed no definite marrow abnormality though it appeared rather hypoplastic. The E.S.R. was 34 mm./1 hour. Further investigations showed no significant change in the blood picture.

A Kepler-Robinson-Power test on 17.10.58 was indicative of Addison's disease: in part 2 of the test the value of A was 21. The urinary output during the day (8 a.m.-8 p.m.) was consistently lower than that during the night (8 p.m.-8 a.m.). For the period 1.12.58-4.12.58 the relationship of day to night urinary output expressed in ml. was as follows: 880, 1394; 598, 750; 1223, 1612; 984, 1278. On 14.10.58 the 17-ketosteroid content of a 24-hour

specimen of urine was 10·3 mg. and on 21.10.58 7·7 mg. The effect of ACTH administration on the steroid content of urine and on the number of circulating eosinophils was tested over a six-day period, 29.11.58-4.12.58. On the first three test days no ACTH was given, and on the second three days 20 units of zinc corticotrophin were given intramuscularly b.d. The urinary output in ml. in successive 24-hour periods over the six days was: 1,370, 2,380, 2,115, 1,340, 2,530, 2,180. The urinary content of 17-ketosteroids in mg. in successive 24-hour periods over the six days was: 3·8, 7·5, 5·5, 6·9, 13·1, 12·1. The urinary content of 17 hydroxycorticosteroids in mg. in successive 24-hour periods over the six days was: 5·7, 6·5, 3·8, 13·9, 27, 47. Daily counts of the number of eosinophils per 100 ml. of peripheral blood over the six-day period were successively: 348, 128, 516, 86, 4, 0. Thus ACTH administration resulted in a twofold increase in urinary 17-ketosteroids, in an eightfold increase in the urinary 17 hydroxycorticosteroids, and in a disappearance in eosinophils from peripheral blood. The daily urinary output of follicular stimulating hormone was 20 mouse units (normal); there was no apparent loss of body hair; and the patient stated that he had not lost his libido.

No evidence of organic renal disease was discovered: examination of urine never revealed abnormal constituents; serum urea was always well within the normal range; urea clearance CM was 72% of average normal; creatinine clearance was 105 ml./min. (normal); and TRP was 85·5%. There was also no evidence of liver dysfunction: representative findings were serum bilirubin, 0·2 mg. %; alk. phosphatase, 13 KA units %; thymol turbidity, 1 unit; flocculation, negative; protein 5·9 g. %; albumen, 3·2 g. %; globulin 2·7 g. %; cholesterol, 113 mg. %.

During the considerable period over which investigations were carried out the patient received no specific treatment for the steatorrhœa. Nor was anti-tuberculous therapy given; the patient claimed that he could not tolerate streptomycin or PAS, and in any case organisms were resistant to the standard drugs. Nevertheless his appetite was good and his strength increased, although he did not gain weight. From 28.12.58 onwards he was given a gluten-free, low fat diet with supplements of vitamin C and vitamin B complex, as well as 2 g. of calcium glycerophosphate t.i.d. On this régime, serum calcium and potassium levels soon returned to normal and his weight by the time of his discharge from hospital on 6.4.59 had gone up from 7 stone 11 lb. to 10 stone 1 lb. However, on 5.4.59 he was still excreting 20·7 g. fat per day. It is proposed to try the effect of ACTH and steroid therapy on fat absorption if the patient can be persuaded to co-operate with anti-tuberculous therapy.

Discussion

The mistake made in diagnosing Addison's disease in 1950 is understandable: although the biochemical tests then available were apparently somewhat equivocal, the complaint of lassitude, the typical skin and buccal pigmentation, and the low blood pressure strongly suggested it. Moreover, the development of pulmonary tuberculosis was in keeping with this hypothesis even although suprarenal calcification could not be demonstrated (Senford and Favour, 1956).

The occurrence of tetany following a bout of diarrhœa at the time of the patient's latest admission to hospital naturally suggested the possibility of

a low serum calcium as a result of steatorrhœa, and when this supposition was verified by biochemical investigation it became apparent that steatorrhœa might be responsible for the signs and symptoms previously attributed to Addison's disease. Low blood pressure is common in cases of steatorrhœa because of loss of water and electrolytes, and perhaps also, as some suggest, owing to associated endocrine disturbance. Moreover, the Kepler-Robinson-Power test may be positive because of a peculiar abnormality in the excretion of a water load. As in the present case, there may be a marked nocturnal diuresis with a corresponding small excretion of water during the day (Wollaeger and Scribner, 1951). There appears to be as yet no satisfactory explanation for this phenomenon. Wollaeger and Scribner (1951) suggested that the poor daytime diuresis may be related to the retention of water in the bowel during the prolonged period necessary for the digestion and absorption of food, but Flear and Cooke (1957) found that the abnormal pattern of water excretion persisted even when fluids were given intravenously.

Increased skin pigmentation sometimes occurs in steatorrhœa, and according to Cooke and French (1958) the buccal mucosa may also occasionally be involved. They cite no examples, however, and indeed this phenomenon seems seldom to have been reported: Thaysen (1932) specifically states that he never encountered it. In the present case the pigmentation was indistinguishable from that of a florid case of Addison's disease. The buccal pigmentation was known to have been present for at least nine years, and the skin pigmentation for at least twenty-two years. However, the eightfold increase in urinary 17 hydroxycorticosteroids in response to ACTH administration excluded the possibility of primary adreno-cortical failure.

It has been shown that hyperpigmentation in bilateral adrenalectomy and in Addison's disease results from increased secretion of melanocyte stimulating hormone (MSH) by the anterior pituitary, that administration of cortisone in these conditions prevents or reduces hyperpigmentation by restoring MSH blood levels to normal, and that MSH is a hormone distinct from ACTH although usually acting in parallel with it (Lerner *et al.*, Shitzume and Lerner, 1954; Sulman, 1956; Sulman and Eviator, 1956).

The sequence of events which leads to the hyperpigmentation sometimes seen in such states as cachexia (Shuster, 1957), cardiac failure (Mickerson and Swale, 1959) and steatorrhœa has not yet been established, but it is thought by many that the essential feature is functional hypocorticalism with compensatory anterior pituitary hyperactivity at least in the early stages of the illness. In the present case the available evidence did not support this theory—urinary corticosteroids were not unduly low and anterior pituitary activity, judged by the urinary content of follicular stimulating hormone and the clinical findings, was within normal limits—but it was not sufficiently adequate to be of significance one way or the other. Boscott and Cooke (1954) have shown that the difficulty so often experienced in achieving saturation with vitamin C in cases of steatorrhœa (as in the present one) is not due solely to poor absorption from the gut, for they encountered it even when the vitamin was given parenterally. They consider it is due partly to a metabolic error

involving also tryosine utilisation, and they believe that this abnormality may be related to the refractory anæmia which sometimes occurs: it may perhaps also be related to excessive pigmentation.

The steatorrhœa in this patient was considered to be due to the malabsorption syndrome, for radiographic appearances were compatible with this and showed no evidence of fistulæ or other abnormality, and pancreatic activity, judging from the normal fat splitting and tryptic activity of the duodenal juices, was apparently not impaired. The onset of pulmonary tuberculosis in 1950 raised the question of a tuberculous ætiology for the intestinal derangement, but, although this possibility could not be entirely excluded, the history, the clinical findings, the results of X-ray investigation, and the persistent absence of tubercle bacilli from the fæces seemed to rule out a frank tuberculous enteritis. It is a fair presumption from the known duration of increased pigmentation in this case that the steatorrhœa was of many years' standing, and during the period of observation in hospital it was fairly gross, the daily fat excretion ranging from 20 g. to 60 g. It is interesting, therefore, that the defect in absorption seemed so selective. There was no clinical evidence of vitamin deficiency, the prothrombin time was normal, there was no anæmia, and the blood sugar curve showed no tendency to flatness. Apart from fat the only serious deficiencies appeared to be in calcium and potassium.

Summary

A case is reported in which steatorrhœa was associated with skin and buccal pigmentation, asthenia, low blood pressure, a positive Kepler's test, and pulmonary tuberculosis. Investigations showed that the adrenal cortex could nevertheless respond adequately to ACTH stimulation. Attention is drawn to the fact that on occasion the presenting features of idiopathic steatorrhœa may easily be mistaken for those of Addison's disease.

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BRONCHOGRAPHY IN PULMONARY TUBERCULOSIS

By N. C. Elphinstone and S. Z. Kalinowski

From St. Wulstan's Hospital, Malvern

The volume of literature about the use of bronchography in cases of pulmonary tuberculosis shows that this investigation has been common practice, but it is difficult to get a clear idea of the indications for the procedure at the present time. An analysis of a recent series larger than any other done with modern media may, therefore, be useful in order to ascertain the various types of abnormality which occur, and to note whether or not they are peculiar to tuberculosis; and to assess the place of bronchography in the modern management of the disease.

Present Series

The series comprises 737 consecutive bronchograms done at St. Wulstan's Hospital in cases of pulmonary tuberculosis between 1953 and 1958. Thirty-seven were technically unsatisfactory, leaving 700 for analysis. Most were done for one of the following reasons:

(*a*) To localise lesions and to determine the extent of bronchial abnormalities before operative treatment.
(*b*) To confirm or exclude bronchiectasis suspected on clinical and/or radiological grounds.
(*c*) In some cases as a complementary procedure to bronchoscopy.

Technique

Apart from a few early cases in which the medium used was iodised oil or sulphonamide-lipiodol suspension, the bronchograms were done with a watery solution of propyliodone. In nearly every case the medium was introduced by cricothyroid puncture, or through the bronchoscope when the combined procedure was carried out (Kalinowski and Lloyd, 1956). Light premedication and local anæsthesia with 2 per cent. butyn sulphate were used. Unlike Domm *et al.* (1956), we found the medium used met all our requirements.

Complications

Any investigation commonly carried out must be reasonably safe, and the medium and methods employed were found satisfactory and safe. Apart from a rise in temperature in some cases of up to 100°, which subsided within 48 hours, complications occurred in only 3 cases (0·4 per cent.).

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One patient developed acute bronchitis with increased sputum from which pneumococci were grown on culture. In the second case pneumonia developed in a bronchiectatic lobe. Both cases responded to antibiotic treatment.

In the third case a radiogram of the chest taken one month after bronchoscopy and bronchogram revealed a spread of tuberculous disease. As the film was taken so long afterwards, the procedure was not certainly responsible, although it is included as a complication.

Perry (1955) wrote on the dangers of bronchography in pulmonary tuberculosis. Two of his patients were found to have tubercle bacilli in their sputum following bronchography with oily media, and in three tuberculous bronchopneumonia was precipitated. Our figures show that the procedure can be safe, confirming the experience of other authors (Don, 1955; Elphinstone *et al.*, 1954; Forgacs, 1955; McCarthy and Misra, 1959; McKechnie, 1953).

Bronchographic Abnormalities

Shaw *et al.* (1954) produced an excellent classification of bronchographic abnormalities in pulmonary tuberculosis, dividing them into three grades. Their classification includes most of the abnormalities found, but does not help greatly from the practical aspect, so the present series comprises the following three groups:

Group 1. Bronchiectasis.
Group 2. Changes similar to those seen in chronic bronchitis.
Group 3. Miscellaneous abnormalities (congenital and cavity-filling).

The first two groups only will be discussed. Cavity-filling has been discussed in a previous paper (Elphinstone and Kalinowski, 1956).

Group 1. *Bronchiectasis*

Difficulty was found in classifying bronchiectasis which has usually been described on bronchographic appearances as fusiform, cylindrical or saccular. However, this classification takes no account of severity, and many of our bronchograms showed bronchi which were certainly abnormal, but could not be included in any of these categories. Bronchiectasis has therefore been divided into four grades, corresponding to the degree of bronchial involvement rather than to the shape of the bronchi.

Grade 1. The normal taper is lost, and the bronchi have a "stiff" appearance. This group may represent early bronchitic changes in larger bronchi and be a precursor of true bronchiectasis.
Grade 2. The walls have a wavy appearance, though the lumen is otherwise of even calibre throughout its course.
Grade 3. This is the cylindrical bronchiectasis of standard classifications in which the bronchi are somewhat dilated.
Grade 4. The bronchi are widely dilated and distorted.

Group 2. Changes similar to those seen in Chronic Bronchitis

Reid (1955) describes the following abnormalities seen in lung specimens from patients suffering from chronic bronchitis injected with radio-opaque material:

1. Absence of peripheral filling due to stenosis of the bronchiolar lumen.
2. Presence of peripheral pooling. The radio-opaque material is pooled in a dilated bronchieole which is usually obliterated beyond the pool.
3. Abnormal peripheral shadows with a spiked outline. The spikes resemble the normal pattern of peripheral filling, but are coarser. They are due to filling of terminal or near terminal bronchioles, further filling being stopped because lung between the spikes is collapsed and fibrosed.

Duprez and Mampuys (1953) investigated the changes occurring in mucous glands situated in the bronchial walls in cases of chronic bronchitis. They describe the following abnormalities on the basis of bronchoscopy, bronchography, examination of fresh post-mortem lung specimens, dried preparations of bronchial casts and serial section.

1. Longitudinal parallel ridges which run from the larynx into the lobar bronchi.
2. Transverse ridges, more numerous in smaller bronchi, representing circular muscle fascicles.
3. Cyst-like structures found in bronchial walls in cases of bronchitis and bronchiectasis, representing dilated mucous glands.

On the basis of these works our second group is divided as follows:

A. Absence of taper, slight irregularity of lumen, and absence of arborization.
B. Peripheral block.
C. Peripheral pools.
D. Ridging (*a*) Transverse, (*b*) Longitudinal } These are grouped together in Table 3.
E. Changes in mucous glands.
   (*a*) Pouching or beading of main bronchi.
   (*b*) Beading of segmental bronchi.

Results

The results are tabulated below and on the following page:

Table 1

Total number of bronchograms	700
Right bronchogram	391
Left bronchogram	309
Completely normal bronchograms	70

TABLE 2.—BRONCHIECTASIS

Right Lung

	Segmental bronchi involved			*Total*
	1 Segment	*2-3 Segments*	*More than 3 Segments*	
Grade 1	21	24	4	49
2	11	8	6	25
3	9	12	15	36
4	2	19	21	43

Left Lung

	Segmental bronchi involved			*Total*
	1 Segment	*2-3 Segments*	*More than 3 Segments*	
Grade 1	8	33	16	57
2	8	3	9	20
3	10	10	23	43
4	1	6	26	33

TABLE 3.—CHANGES SIMILAR TO THOSE SEEN IN CHRONIC BRONCHITIS

	Right lung	*Left lung*
A	199	173
B	88	73
C	5	4
D	29	34
E	102	173

Discussion

The percentage of abnormal bronchograms (90%) is higher than in other reported series. Rabinowitz and Harper (1951) reported 83% abnormal; Don (1955) 78·2%; McLeod (1958) 78%; and McCarthy and Misra (1959) 68%. Other authors have given lower figures. The selection of our cases and the inclusion of slight abnormalities probably accounts for this.

In Table 2 abnormalities affecting major and segmental bronchi are compiled together. The extent of the bronchial abnormalities corresponded closely with the degree of pulmonary involvement. Minor changes (Grades 1 and 2) were found in segments which at the time of bronchography were clear of disease radiologically, but in which infiltration had previously been present. Grades 3 and 4 were seen mainly in contracted fibrotic segments, and in totally destroyed parts of the lung.

Grades 1 and 2 were frequent, as Table 2 shows, but the patients were nearly all symptom free. However, some were subjected to resection only because of the bronchial changes, and this may not have been necessary. Resection was usually advocated in cases in which residual tuberculous lesions were seen radiologically in bronchiectatic segments, and was sometimes wider than seemed indicated by the extent of residual pulmonary disease.

It was interesting to find so many changes originally described as typical of chronic bronchitis. Twenty-five per cent. of the patients were bronchoscoped, and as no evidence of tuberculous endobronchitis was seen in any case, it is postulated that the cause of the lesions is probably mechanical in tuberculosis as in chronic bronchitis, and not due to tuberculous endobronchial disease. Reid (1955) also stated that the pathological processes accounting for the bronchographic appearances are not exclusive to chronic bronchitis.

The additional knowledge gained from these bronchograms was mainly academic, and rarely essential in planning treatment, except for localisation of lesions in a few cases. Lateral tomography was usually done pre-operatively, and usually gave as much help as bronchography.

Conclusions

Our conclusions are that although the percentage of abnormal bronchograms is high (90 per cent.), the value of bronchography in pulmonary tuberculosis is very limited, as was found by Forgacs (1955). Its main use is in localisation of disease before operation, although it does not seem to be superior to lateral tomography for this. The changes were not specific for tuberculosis.

It would be of great academic interest to follow up the high proportion of patients showing changes associated with chronic bronchitis, to find out whether or not after arrest or cure of their tuberculosis they will develop the typical picture of chronic bronchitis; and if not, whether bronchograms will revert to normal.

Summary

Seven hundred bronchograms done on patients with pulmonary tuberculosis are reviewed. Particular notice was taken of evidence and degree of bronchiectasis, and of chronic bronchitic changes.

No changes were seen peculiar to tuberculosis.

The results do not show that the procedure is an important aid to treatment in pulmonary tuberculosis, the main value being localisation of lesions before surgical treatment.

Bronchitic changes were noted in a high proportion of cases. It is suggested that a follow-up of these patients would be interesting.

We should like to thank Dr. T. W. Lloyd for his encouragement, and Miss D. Moore who was responsible for the radiography.

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SPONTANEOUS PARALYSIS OF THE PHRENIC NERVE

WITH A SPECIAL REFERENCE TO CHRONIC PULMONARY TUBERCULOSIS

By Samir K. Gupta

From the Islington Chest Clinic and Whittington Hospital, London

Before the introduction of chemotherapeutic agents for the treatment of pulmonary tuberculosis, phrenic nerves were deliberately crushed to cause a temporary paralysis of the ipsilateral half of the diaphragm. Sometimes permanent palsy followed (Pagel *et al.*, 1953). The same phenomenon may occur spontaneously in cases of chronic pulmonary tuberculosis, but there is no reference to this association in the standard textbooks on diseases of chest (Goldberg, 1947; Myers and McKinlay, 1948; Marshall and Perry, 1952; Ellman, 1952; Pagel *et al.*, 1953; Hinshaw and Garland, 1956), and I could trace only one published case report in the British literature (Corrigan and Dworschak, 1953).

The purpose of this paper is to describe 8 cases of hemi-diaphragmatic paralysis occurring in tuberculous patients. An attempt is also made to explain the possible mechanism and pathogenesis.

Case Reports

Case 1. A man aged 60 had had chronic fibrotic tuberculosis of his lungs since 1941. While receiving chemotherapy for a relapse of his pulmonary condition he developed an asymptomatic palsy of his left phrenic nerve in May 1957, which has persisted to date.

There were no malignant cells in the sputum and bronchoscopy was negative. He has since remained well.

Case 2. A man aged 62 contracted pulmonary tuberculosis in 1945. Acute exacerbation of his co-existent chronic bronchitis necessitated admission to hospital. During one of these episodes he was found to have a paralysed right phrenic nerve which was confirmed by screening (August 1957). He was thoroughly investigated for a possible bronchial or gastric neoplasm (by bronchoscopy, sputum examination, and barium meal and follow-through examination, etc.).

His chest X-ray has not significantly altered since August 1957. His general condition was good and his weight was steady when last seen in June 1959.

Case 3. In 1957 a 48-year-old man was admitted to hospital with some infiltration in the left upper zone. The left hemi-diaphragm was elevated and the screening confirmed paralysis. Though his sputa contained acid-fast bacilli, he was transferred to a thoracic surgical unit because of the possibility of a co-existent neoplasm.

Though he improved very much clinically on anti-tuberculous drugs the

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left nerve remained paralysed. Bronchoscopy report was " a stricture of the left lower lobe bronchus." The appearance was suggestive of malignancy and he was thought to be inoperable. A biopsy report, however, showed some chronic inflammatory process only and, following a second bronchoscopy a few months later, the biopsy report was identical.

He has been kept under close supervision since. He is well and his X-ray appearance has remained unchanged. He was last seen in May 1959.

CASE 4. A man aged 32 had been suffering from pulmonary tuberculosis since 1947 and had been treated by bed rest alone. He had some concurrent lymphadenopathy in the right side of his neck.

The chest X-ray, taken during the initial illness, also showed " a paralysed right hemi-diaphragm." He came under observation in January 1959 because of some fibrotic disease in his right lung.

Because of the long history and excellent general condition neoplasm was not considered as a possibility in this case and bronchoscopy was not carried out. His W.R. and Kahn tests were negative. He had no history suggestive of diphtheria, poliomyelitis or polyneuritis.

CASE 5. A man aged 72 first attended the chest clinic in May 1957 because of a persistent productive cough for four months. His general condition was poor. The chest X-ray showed an opacity in the left lower zone with a raised hemi-diaphragm; there was some fibrosis at both apices and some hilar calcification on the right side. Screening confirmed paralysis of the left phrenic nerve.

He had a small empyema on the left side. Pneumococci were found in the pus and he responded satisfactorily to antibiotic therapy and repeated aspiration. Sputum, however, contained acid-fast bacilli and he was simultaneously treated with antituberculous drugs. The opacity above the left hemidiaphragm persisted, although much reduced in size. Numerous sputa failed to show any malignant cells. In hospital his general condition improved and he gained 10 lb. in weight in six weeks. Bronchoscopy was undertaken and the report was: " Left intermediate stem bronchus shows inflammation and this area bleeds easily. Some pus is coming from lower lobe." A biopsy was taken and revealed a chronic inflammatory change.

He has been attending the follow-up clinic regularly and when last seen in September 1959 he was well. The hemi-diaphragm was still paralysed.

CASE 6. A woman 40 years old contracted pulmonary tuberculosis in 1946. She had a relapse in 1955 when her sputa showed acid-fast bacilli again. During this period an elevated right hemi-diaphragm was noticed. On reviewing her earlier films, however, it was obvious that the phrenic nerve had been paralysed as early as 1949.

Because of the long history and excellent present health the possibility of neoplasm of a bronchus has been ruled out. The right phrenic nerve is still paralysed on screening.

CASE 7. A 33-year-old man was admitted in September 1951 following sudden hæmoptysis. The chest X-ray showed gross tuberculous infiltration of both lungs, involving specially the upper and middle zones and his sputum contained acid-fast bacilli.

He was treated with daily streptomycin and PAS. There was marked clinical improvement.

During this period the level of the left hemi-diaphragm appeared to rise and screening confirmed paralysis. In 1953 a two-stage thoracoplasty was undertaken on the right side, because of relapse of the tuberculous process. He had remained under our care since 1954. The patient is well at present. Recent screening confirmed the paralysis. Because of the long history and excellent general condition the possibility of neoplasm has been ruled out.

CASE 8. A 57-year-old woman was admitted to the hospital in 1958. She had a high pyrexia, swollen ankles and a productive cough, was very emaciated and had fainting attacks. She had also signs of a right-sided pleural effusion. In the past she had suffered from Raynaud's phenomenon, but she had never had any injury or operation in the neck. The chest X-ray showed consolidation of the middle and lower lobes on the right side with an effusion at the right base. Bronchoscopy was undertaken in November 1958. The report was: "No evidence of bronchial carcinoma; some muco-pus in the right bronchial tree." A trap specimen was sent for malignant cells but none were found, although acid-fast bacilli were discovered.

A laryngoscopy was undertaken and she was found to have right recurrent laryngeal nerve paralysis. A Rose-Waaler test was negative.

She was treated with anti-tuberculous drugs plus steroids (prednisolone 20 mg. daily). During her stay in hospital her right hemi-diaphragm showed a considerable rise and screening confirmed paralysis in November 1958. There was also some evidence of a radiological spread of the tuberculous process in the upper part of the right lung, but ultimately there was marked resolution with some residual fibrosis in the right lung.

The patient developed a right-sided ptosis shortly before her discharge, but she had no enophthalmos or miosis. She was last seen in August 1959 when she was well and continuing to receive the anti-tuberculous chemotherapy.

In none of these 8 cases was an evident cause of the phrenic palsy discovered. No history of any operation in neck or thorax was given by any patient. In some the diagnosis of an inoperable neoplasm of bronchus was made but later refuted. A number of other laboratory investigations, including W.R. and Kahn tests, were negative.

Discussion

These cases suggest that phrenic palsy in association with chronic pulmonary tuberculosis is not so rare, as suggested by the literature. There are only a few published reports in the continental press of this syndrome (Zappia, 1935; Berki and Meggyessy, 1937; Grobli, 1944; Giraud, 1957) and one in the Canadian literature (Corrigan and Dworschak, 1953). Before incriminating pulmonary tuberculosis it is essential to exclude the other possible causes (Table I). Even in tuberculous cases the exact mechanism is uncertain and there is no published autopsy report.

TABLE I.—CAUSES OF PARALYSIS OF THE PHRENIC NERVE

Usually permanent	*Usually transient*
Diseases involving the centre and the spinal cord:	Pneumonia and lung abscess (Freedman, 1950)
Poliomyelitis (Abels and Leiner, 1944)	Subphrenic abscess (Harley, 1949)
Hæmorrhage into the cord	Pleural effusion (Meyler and Huizinga, 1950)
Tumours of the cord and its meninges	Phrenic neuritis:
Diseases of the cervical spine	? Toxic (Freedman, 1950)
Myelitis	? Viral (Kahn, 1953)
Herpes zoster (Halpern and Covner, 1949)	Pulmonary infarction (Macleod and Grant, 1954)
Motor neurone disease (Brain, 1955)	Prophylactic inoculations (French, 1938; Miller and Stanton, 1954)
Trauma	
Other causes affecting the phrenic nerve:	
Polyneuritis, mostly lead and diphtheria	
Wounds in neck	
Birth trauma (Erb's palsy)	
Neoplasm (specially bronchial)	
Rarely in aortic aneurysm (Sanguinetti and Galzerano, 1943)	
Neuro-syphilis	

ENLARGED LYMPH NODES AND PRESSURE

Grobli (1944), reporting a single case, remarked that hilar adenopathy probably caused the paralysis of the ipsilateral phrenic nerve. He suggested that the left nerve should be more frequently involved as it was more intimately related to the hilar nodes than the right one. Corrigan and Dworschak (1953), also reporting a single case, denied the importance of glandular pressure. Their patient was a child aged 2 years, with extensive fibro-cavitary disease of the left lung. The left phrenic nerve did not become paralysed until the child had received six months' chemotherapy. Hence they argued that tuberculous (*i.e.* fibrotic) involvement of the nerve was a more plausible explanation of this exceptional syndrome. They could not find a single case of hemidiaphragmatic palsy in children suffering from classical primary tuberculosis.

Unlike the left recurrent laryngeal nerve, the phrenic nerves take a more superficial course in the thorax and are not intimately associated with any group of mediastinal lymph nodes (Gray's Anatomy, 1956). Even in cases of laryngeal palsy associated with chronic pulmonary tuberculosis, the factor of glandular pressure has been overstressed (Gupta, 1959). In the present series none of the patients had been suffering from primary tuberculosis, but cervical adenopathy might have played some role in Case 4.

POST-INFLAMMATORY FIBROSIS AND CHRONIC MEDIASTINITIS

The role of this factor has been stressed in the syndrome of laryngeal palsy in chronic pulmonary tuberculosis (Gupta, 1959). The phrenic nerves are not intimately related to the lungs, but may become involved in pathological conditions affecting the lungs (Wense, 1955). Thus, in a case where exploratory thoracotomy was undertaken for a suspected neoplasm, the paralysed phrenic nerve was found to be œdematous owing to the inflammatory process in the adjacent lung (Wense, 1955). Peripulmonary fibrosis and adhesions are usually found at post-mortem in chronic pulmonary tuberculosis (Pagel *et al.*,

1953). Perineural fibrosis, causing paralysis of certain nerves, has also been observed at autopsy of tuberculous patients with pneumoconiosis (Arnstein, 1941).

All patients in the present series had been suffering from chronic pulmonary tuberculosis and many of them had extensive disease at one time. There was marked clearing and resolution of disease with treatment, but most of them showed evidence of fibrosis in the chest X-ray (as distortion of trachea, aortic knuckle and heart shadow, etc.). Cases 5 and 8 in this series need special emphasis. The former patient had a small pneumococcal empyema in the left side of his chest over and above his tuberculous infection of the underlying lung. The active inflammatory process was entirely confined within the lower half of the lung and the ipsilateral phrenic nerve may have become involved by the local inflammatory œdema and fibrosis. Case 8 was even more striking. The lower part of the right lung was at first involved in the tuberculous process and the ipsilateral phrenic nerve was at first paralysed. Shortly afterwards the disease spread to the upper part of the same lung and the patient was found to have a right recurrent laryngeal nerve paralysis. The simultaneous onset of ptosis might have been due to the involvement of the ipsilateral sympathetic fibres. Since the utmost care has been taken to exclude a malignant process, the only logical explanation of this phenomenon is based on a local inflammatory process. A strikingly similar case (though due to some non-tuberculous pneumonia) has been recorded by Freedman (1950).

Since fibrosis is the characteristic feature of a chronic tuberculous process it is unusual to find involvement of nerves during the acute phase or in those who have acute, exudative disease (Corrigan and Dworschak, 1953; Gupta, 1959). Once the fibrotic process starts it is persistent, so that the nerves, once paralysed, do not regain their function. In non-tuberculous inflammation of the lung the process is usually reversible, so it is not surprising to find that the paralysis of phrenic or recurrent laryngeal nerves tends to be temporary (Freedman, 1950).

Other Possible Mechanisms

Grobli (1944) has suggested that paralysis of the diaphragm might represent a defensive reaction of the muscle itself if the surrounding viscera are inflamed (*cf.* in peritonitis, sub-phrenic abscess), but screening never shows paradoxical movement unless the phrenic nerve is also paralysed. The " sympathetic immobilisation " is usually temporary and disappears as the primary condition subsides.

Kahn (1953) described a temporary palsy of the right phrenic nerve in a patient with chronic pulmonary tuberculosis. The onset was acute with a sudden febrile illness and he postulated a " phrenic neuritis " of viral origin. None of the patients in this series had a similar episode.

A hypothetical toxic factor has been suggested by several authors, but there is no proof of its existence. Moreover, there is no reason why toxic neuritis should affect the phrenic nerve alone, which is normally so resistant to the

different forms of toxic and nutritional neuritis (Brain, 1955). Freedman (1950) has given an excellent account of this syndrome, occurring in non-tuberculous inflammation of the lung. He also thought that the toxic neuritis of the ipsilateral nerve was the decisive factor in these cases. Some common features were observed in all his cases, namely a latent interval of several weeks between the onset of illness and the paralysis, inflammatory involvement of lower part of the ipsilateral lung, and in some cases return of function of the paralysed hemi-diaphragm, following complete resolution of the inflammatory process. One of his patients had also left upper zone inflammation and, interestingly, was found to develop a left recurrent laryngeal nerve palsy in addition to a paralysed left hemi-diaphragm. All this evidence points strongly towards a basic local factor, *i.e.* post-inflammatory fibrosis, as a cause of paralysis.

Rees-Jones (1944) has described this syndrome in association with cystic disease of the azygos lobe. He suggested a possible developmental anomaly in which the phrenic nerve could get involved in the azygos lobe. On reviewing his data, however, one cannot exclude co-existent apical tuberculosis in his case.

Summary

Eight cases of paralysis of phrenic nerves are described. All these patients had been suffering from chronic pulmonary tuberculosis. The possible mechanism of this association is discussed and special stress is laid on post-inflammatory fibrosis and chronic mediastinitis. One of the cases described had recurrent laryngeal nerve palsy in addition to ipsilateral hemi-diaphragmatic paralysis. The literature is reviewed.

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Brit. J. Dis. Chest (1960) **54**, 290.

PHILIP ELLMAN

THIS number of the Journal opens on a particularly sad note in having to record the death of its Editor—Philip Ellman.

Of the many achievements in his full life few gave him as much satisfaction as guiding this Journal through a period of change, and he has left us with the knowledge that its reputation and fame have been firmly established in its new form. This success was principally due to his personal efforts in knowing where new subject matter was to be found, in seeking new contributors and, with an enlarged Editorial Board, ensuring that a high standard of published work was maintained. Many young authors owe a great debt of gratitude to Ellman for his encouragement and help, without which many valuable contributions might not have seen the light of day. It was most fitting that the Golden Jubilee of the Journal was celebrated in 1956 during his tenure of office, and to recall how the success of his editorship was acknowledged by his fellows.

Ellman's medical career started in Manchester, where he qualified at an early age before migrating to London, where he held junior hospital appointments, including one at Colindale which stimulated his interest in chest diseases. This, from force of circumstances, was continued in Switzerland, where he made the first of a number of original contributions and where, incidentally, he obtained a doctor's degree. It is possible that Ellman would have elected to become a general physician, but his experience and qualifications led him into chest work, which was one of the two branches of medicine wherein he made his name. His other speciality was rheumatic disease, in which his interest had been stimulated by his association with Sir Leonard Hill. He joined the staff of the special unit which had been founded by the L.C.C. in St. Stephen's Hospital in the pre-war years and was an active leader in investigation and research into the difficult problems encountered. It is said that the term " rheumatoid disease " was originated by him and certainly the association of chest lesions with the rheumatoid state was first adequately described by him. He taught well, and both undergraduate and post-graduate students will remember his concise and often didactic approach.

His enthusiasm for organization and teaching was also well known in East Ham and the chest units with which he was associated. He modelled his approach on that of his mentors—the great partnership of Sir Robert Young and Dr. G. E. Beaumont—with the patient rather than the disease as the centre. When he gave an opinion it was clear cut and concise, not taking refuge behind a mass of verbiage or woolly thought. Many thoracic surgeons will recall with gratitude his appraisal and prognosis of patients when sent for further advice. These patients were his friends and not impersonal subjects of a case record, and it was on this basis that he practised medicine.

Such are the brief outlines of a career that finished all too soon, but they can tell little of the man. The most noticeable thing about Philip Ellman was his vitality and assurance. A small man, very erect, he had an almost birdlike

PLATE XVIII

PHILIP ELLMAN

To face p. 290

quality of interest and curiosity concerning anything that came his way. It was impossible to be bored in his company, and his insatiable desire to know what was going on everywhere made him, a little unexpectedly, an excellent listener drawing out the smallest details of a subject that interested him. But he was by no means always a listener; he could talk freely and at length, and in argument his opponent would have to be very quick to counter his attack. He enjoyed debate and argument as something which sharpened the wits, and at the end of a possibly slightly warm encounter he would put his hand out with his head on one side to say with a charming smile that he had really agreed all the time.

As has been said, he wrote freely and well, and many of his communications on chest disease and rheumatoid disorders are well known. The book *The Essentials in Diseases of the Chest*, written for general practitioners and students, had the same incisive touch as his clinical teaching, and the quality of his writing is well known to readers of this Journal.

Any appreciation of Philip Ellman based only on his professional capabilities would be useless without reference to his family life. He had a wonderful capacity for inspiring friendship, and even with all his activities his home life with his family seemed fuller than most. He loved living outside London and getting the best of both town and country life, and it was his zest for living that made him such an attractive man to meet in any capacity. His courage was superb and never shown to greater advantage than in his last distressing illness, which he bore without complaint.

Philip Ellman had possibly fewer opportunities than his talents merited, but such chances as came his way he took with both hands and developed them into something lasting. The profession will remember him for three things—his interest in chest disease and in rheumatoid conditions and as Editor of this Journal. Those who knew him personally will recall with gratitude his friendliness and courtesy, his bursting enthusiasm and energy, and will realise that ambition does not have to go with self-seeking, nor a restless spirit with discontent. He made a worthwhile contribution to life as well as to medicine.

T.H.S.

Brit. J. Dis. Chest (1960) **54**, 292.

REVIEWS OF BOOKS

17TH AND 18TH CONFERENCES ON THE CHEMOTHERAPY OF TUBERCULOSIS

Held by the Veterans' Administration Armed Forces

Each year the Veterans' Administration Department of Medicine and Surgery in the United States holds a conference on the treatment of tuberculosis, especially chemotherapy, although other subjects of a similar interest are dealt with. The main object of the conferences is to receive the reports on the pilot studies organised by the Veterans' Administration to deal with the solution of specific problems. The committees draw up a very carefully planned scheme of research in as great a detail as possible, and the plan when it is completed is sent to various selected hospitals under the Veterans' Administration, who carry out the field work. The results of this are collected, then sorted out by the committees, who report in due course to the conference whose transactions we are considering. The method has the great advantage that a very large number of cases come within the net. On the other hand, it does seem that the supervision carried out by the committees is rather less rigorous than that carried out in the M.R.C. trials in Great Britain. Another difficulty under which they labour is that in the Veterans' Administration Hospitals the rate of irregular discharge is very considerable. Where the results are clear-cut this is probably of not very great significance, but it imposes a considerable handicap when the answers to the questions are more equivocal.

In addition to these official reports a large number of papers by other workers are presented and reported. In the 17th Conference report investigation of 628 cases dealt with the comparative therapeutic efficiency of daily streptomycin/isoniazid compared with isoniazid/PAS in patients with no prior chemotherapy; and also whether the addition of a third drug, daily streptomycin/PAS, contributes anything to the therapeutic efficiency, considering the factors of toxicity and emergence of resistance. From the figures available there was no appreciable difference in therapeutic efficiency among the three régimes as measured by X-ray change, conversion of sputum and cavity closure. Possibly less resistance developed in the isoniazid, daily streptomycin régime, though streptomycin toxicity caused discontinuation of treatment in 11 per cent. of the cases. The total incidence of toxicity was far greater on the triple drug régime than with the others.

Therapeutic efficiency of cycloserine in combination with isoniazid was compared with that using isoniazid/PAS. The results were considered among 405 patients at four months, and 182 at the end of eight months of treatment. The tentative conclusion was that this régime appeared less efficient than the isoniazid/PAS, but the toxicity produced by using 0·5 g. of cycloserine in two divided doses was negligible.

To compare an isoniazid/pyrazinamide régime with isoniazid/PAS, the pyrazinamide was given in a 3 g. daily dosage; no significant therapeutic superiority was found, and the pyrazinamide toxicity was three times that of PAS. It was concluded that pyrazinamide was a suitable drug to combine with isoniazid in patients unable to tolerate PAS, provided that it was only used

in hospital under competent supervision, including regular liver function tests. An indirect comparison of isoniazid/pyrazinamide with isoniazid/cycloserine infers that the pyrazinamide may exceed the cycloserine in therapeutic value.

An interesting report was on the prevalence of streptomycin resistant, PAS resistant, and isoniazid resistant tubercle bacilli among previously untreated patients. Among the 3,161 patients admitted between September 1956 and August 1957, 2·8 per cent. were resistant to streptomycin, 2 per cent. had PAS resistant bacilli, and 3 per cent. had isoniazid resistant bacilli. This compares with a figure of 2·6 per cent. revealed in a similar investigation in 1952 as regards streptomycin resistant bacilli.

Tests undertaken on streptovarycin in ten study units to ascertain its toxicity determined its effectiveness in retarding the development of resistance to isoniazid. It was used in a single dose of 3 g. per day orally. It seemed doubtful whether it delayed the emergence of resistance to isoniazid. In the dosage used there was no greater therapeutic efficiency than might be achieved by isoniazid alone, and toxicity due to it required its discontinuation in 9 out of 26 patients.

In the report on the 18th Conference a comparison of the therapeutic efficiency of daily streptomycin/isoniazid, isoniazid/PAS, and daily streptomycin/PAS/isoniazid, in 1,150 patients confirmed previous reports. Comparison between the toxic effects of streptomycin and streptomycin pantothinate on eighth cranial nerve toxicity showed no significant difference. A report from Chicago suggested that under certain circumstances the toxic effects of high doses of cycloserine on the central nervous sytem can be controlled by concomitant administration of sedatives, anti-convulsants, tranquillising agents and pyridoxine, singly or in combination.

There was a very interesting report on the genetic aspects of isoniazid inactivation in 20 families, comprising 40 parents and 79 children. From these data it was concluded that isoniazid inactivation pattern is a hereditary trait, that it is not sex linked, that rapid inactivation is probably inherited as a Mendelian dominant and slow inactivation as a simple Mendelian recessive.

Doubts were shown on the value of kanamycin in a study of 75 patients with advanced cavitated disease, and whose organisms were resistant to streptomycin and isoniazid. This had to be abandoned since 65 of the 75 patients were lost prematurely; 29 due to auditory toxicity, 8 to irregular discharge, 5 to pain at the injection site, 3 to X-ray worsening and 3 to death from tuberculosis; the remainder for miscellaneous reasons.

It is usually considered that there is little risk that patients with genito-urinary tuberculosis will infect other members of the household, but investigations showed that the children of patients with genito-urinary tuberculosis react to tuberculin three times as frequently as would be expected. In addition, all the positive tuberculin reactors were in families with only 28 per cent. of the patients with genito-urinary tuberculosis; families of all patients with pulmonary tuberculosis in addition to genito-urinary tuberculosis were excluded.

A curiously similar result was noted in a study on airborne infection by comparing " drug susceptibility patterns " of organisms recovered from guinea pigs with the " drug susceptibility patterns " of patients in the experimental ward at the time airborne infection is believed to have taken place. It was possible to determine that 19 of the 22 guinea pigs infected over a two-year period could be traced to just 2 of the 62 patients.

Each of these volumes contains about 400 pages of reports on various researches and naturally they are of somewhat uneven quality. Many of the papers will be read with very great interest by those interested in tuberculosis and its treatment.

F. H. YOUNG.

Social Work in Tuberculosis. By MARGARET COLTART, M.A., A.M.I.A., Head Almoner, Brompton Hospital, London; HELEN RAINE, B.A., Social Science Cert., Tuberculosis Welfare Officer, Middlesex County Council; and ELIZABETH HARRISON, Joint Editor, N.A.P.T. Handbook of Tuberculosis Activities. Pp. 144.

The authors must be congratulated on this contribution to the literature on social medicine. Concise, yet not without detail, it makes easy and interesting reading.

Having been concerned for over twenty-five years with medical and social work in relation to tuberculosis, I have yet learnt something from this book and quite appreciate how invaluable it will prove not only to medical but to all social workers entering into this fascinating branch of the Health Service. Only by combining the medical and social sides can good results be achieved and the examples given in this book illustrate how essential is integration.

I would like to see this small compendium of knowledge and experience in the hands not only of medical and social workers, whatever their speciality, but also in the hands of all administrative officers in the Health Service, in order to achieve better and closer co-operation between all its branches.

F. M. WILLIAMS.

Automatic Ventilation of the Lungs. By WILLIAM W. MUSHIN, M.A., M.B., B.S., F.F.A.R.C.S., L. RENDELL-BAKER, M.B., B.S., F.F.A.R.C.S., and PETER W. THOMPSON, B.A., M.B., B.Chir., F.F.A.R.C.S. Oxford: Blackwell Scientific Publications. 1959. Pp. 349. Illus. 47s. 6d.

This is a very good book and should be of value to anyone who elects or is forced to give artificial ventilation. The major part of the book is devoted to a description of the mechanisms and functional properties of fifty-six different types of automatic ventilator and five manual ventilators. The ingenuity of their design is quite remarkable and makes interesting reading for anyone with a mechanical bent. For people directly concerned with their use the analysis of their functional properties should prove particularly useful. Tank and cuirasse respirators are not discussed.

The opening chapters of the book deal with the physiological, clinical and physical aspects of controlled ventilation. The physiological aspects are clearly and concisely described and the information has been carefully selected for its relevance to the subject. The effect of positive pressure inflation upon ventilation-perfusion relationships in the lung might have been stressed, since the increase in the difference between end-tidal and arterial P_{CO_2} which this produces results in error in the assessment of ventilatory status from end-tidal sampling.

The chapter on the clinical aspects of controlled ventilation would have been improved by a discussion of the problems of assessing adequacy of ventila-

tion by the measurement of body CO_2 levels, though at the time this book was written there was no simple method of making such measurements generally available.

The authors conclude with a reminder that man-made automatic machines merely aid and are no substitute for the most complex of programmed computers—the skilled anæsthetist.

J. B. L. HOWELL.

British Medical Bulletin, Volume 16, No. 1, January 1960. London: Medical Department, British Council. Pp. 88. 20s.

This British Council Bulletin reviews various aspects of antibiotics currently used, together with some consequences of their misuse. Much of it is already well known, although there can be no harm in restating the broad principles governing the use and abuse of antibiotics. So far the most spectacular, but perhaps not the most fundamental, advances in knowledge have come from bacteriologists and similarly orientated clinicians. It is clear that the chemist is also deeply committed and that his contributions may, in due course, prove the most decisive in our understanding of the action and hazards of antibiotics and in providing new and effective ones. The chemical approach in this issue is certainly the most refreshing and stimulating, commencing with an interesting classification of antibiotics based on their chemistry, discussing the nature of the selective toxicity of antibiotics and ending with the search for new ones. Sandwiched between these vivid articles are the usual ones on how to use antibiotics wisely, their pharmacology, their dangers, drug resistance, combinations, and the role of the laboratory. Specific clinical uses are restricted to straightforward accounts of tuberculosis, subacute bacterial endocarditis, and indications for prophylactic use of antibiotics in medicine and surgery, a happy selection for readers of this particular journal.

J. G. JAMES.

The following books have been received and reviews of some of them will appear in subsequent issues.

The Health of Business Executives. Transactions of the Conference held in the Royal Festival Hall, London, 1959. London: The Chest and Heart Assocn. Pp. 128. 15s.

Tagungsbericht zum 9 Kongress der Süddeutschen Tuberkulosegesellschaft in Passau, Mai 1959. Dr. Friedrich Kreuser, Winnenden. Stuttgart: Georg Thieme. Pp. 204. DM. 13.50.

Principles of Bone X-ray Diagnosis. George Simon. London: Butterworths. Pp. 170. Illus. 57s. 6d.

Diagnosis and Treatment of Diseases of the Trachea and Bronchi. Herman J. Moersch and Howard A. Anderson. Charles C. Thomas, Illinois, and Blackwell Scientific Publications, Oxford. Pp. 108. Price 34s.

Die Asbestose der Lungen. Genese—Klinik—Rontgenologie. Dr. Med. H. Bohlig, Dr. Med. G. Jacob and Dr. Med. H. Muller. Stuttgart: Georg Thieme, Pp. 166. DM. 59.40.

Brit. J. Dis. Chest (1960) **54**, 296.

REPORT

PATIENTS' WAITING-TIME

Organisation of a Chest Clinic*

Patients' waiting-time is one of the points discussed in a Ministry of Health report. This is the latest in a series of studies of hospital organisation and methods and discusses the details of organising the flow of patients at chest clinics, the design of an out-patient appointments system and the clerical practices needed to support these arrangements and to maintain the necessary medical records.

The report states that the great bulk of matters dealt with is concerned with efficiency of a fairly mechanical kind. It is recognised that this efficiency ranks only second in importance to the standard of medical and nursing care which is given to the patients. These two aspects are not, however, conflicting but complementary.

It was found that the minimum time each " old " patient spends at a chest clinic after the first visit cannot be much less than half an hour, because it is fairly general practice for the patients to wait for consultation until the " wet " X-ray film is ready, and films take about twenty minutes to process. A reasonable minimum waiting-time for " new " patients is about an hour. These times are achieved at some clinics with some of their patients, but others are obliged to spend from two and a half to three hours on the premises (with no special justification, such as an additional X-ray, to account for the difference).

Unnecessary waiting-time contributes to congestion in waiting rooms, passages, etc. If space is limited, patients suffer overcrowding, inconvenience and discomfort, and the risks of infection being passed from one to another are increased.

The main cause of avoidable waiting-time is that the call-up and movement of the patients through the various stages in the clinic procedure are not properly related to any physical limitations of the accommodation in which the clinic is housed. These may remain even after measures are taken to ensure that the accommodation is used to maximum advantage. If consultation clinics are to run smoothly it is necessary to measure both the capacity of the various parts of the accommodation through which the patients have to pass and the time it takes the staff or the patient to carry out each part of the procedure, and to organise the clinics in the light of these facts.

The evidence of the time studies shows that the times taken at the various stages of the procedure at chest clinics do not vary greatly as between patients. Even the times needed for medical consultations are carried out at a fairly constant rate, although a distinction has to be made between new and old patients at some stages. It was quite possible to decide on average times for the purposes of organising a smooth and even flow of patients.

The studies showed that the majority of patients arrived early rather than late, but that the rate of non-attendance was high.

The report states that the aims of a good and effective appointments system in a chest clinic are not only to spare the patients unnecessary waiting, but thereby also to encourage a higher level of attendance.

* Hospital O. and M. Service Reports No. 3, Chest Clinics. H.M.S.O. 1s. 9d. net.

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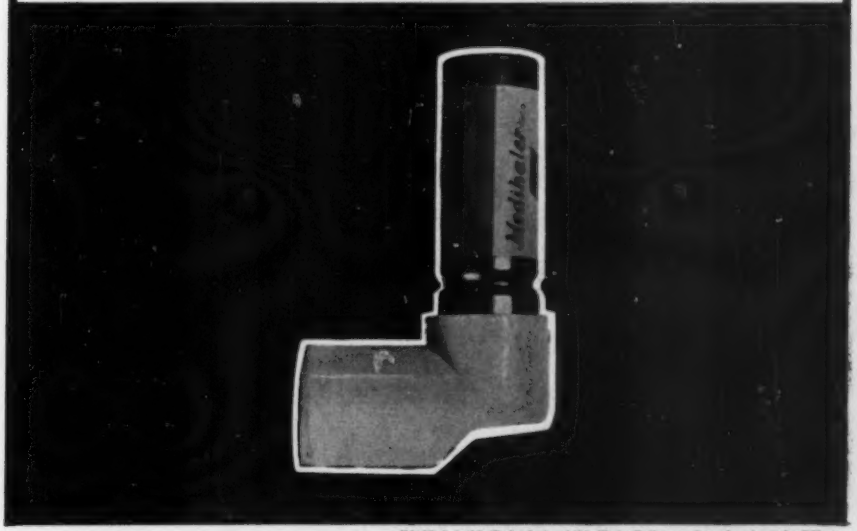

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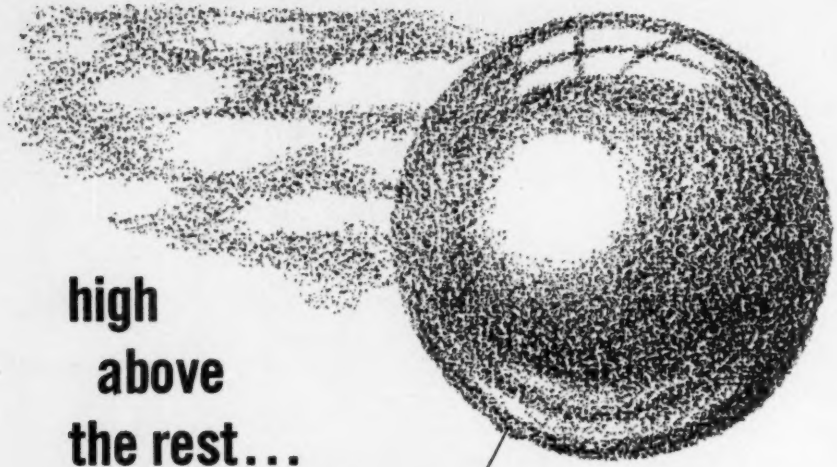

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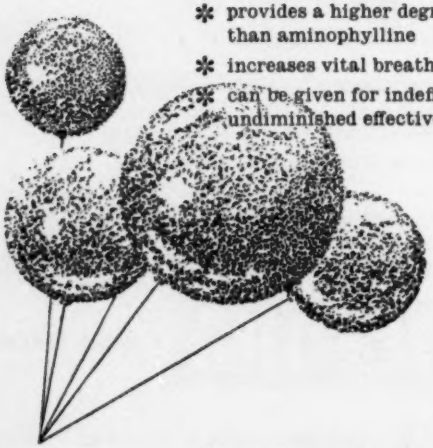

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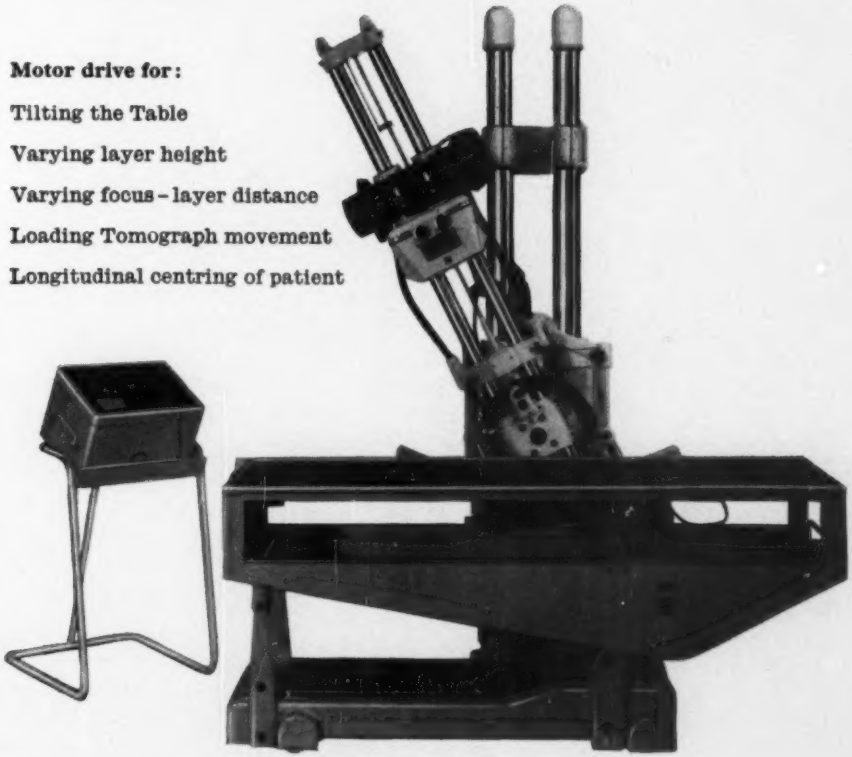

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By Victor A. McKusick, M.D.
Associate Professor of Medicine, The Johns Hopkins University School of Medicine

Beginning with a critical survey of cardiovascular sound, the author explores every phase in heart sound. Murmurs of various types and other specific disorders are covered. There is a chapter on physiologic, pharmacologic, physical and other procedures employed in the investigation of cardiovascular sound in man. Chapters on cardiovascular sound in animals and on lung sounds are also included. Throughout the book, spectral phonocardiography, a recent development, is used.

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